

PATENT SPECIFICATION

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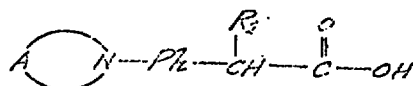
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(54) TERTIARY AMINO ACIDS, PROCESS FOR THEIR MANUFACTURE AND COMPOSITIONS CONTAINING THEM

(71) We, CIBA-GEIGY AG, formerly Ciba Limited, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
 The present invention provides α - (amino - phenyl) - aliphatic carboxylic acids, in which the amino group is a cyclic *tert.* - amino group, having the formula



(I)

in which R₁ represents a hydrogen atom or a lower alkyl, cycloalkyl or cycloalkyl - lower alkyl group; Ph represents a phenylene radical or a phenylene radical substituted by one or more of the same or different substituents selected from lower alkyl, free hydroxy, free mercapto, lower alkoxy, lower alkyl - mercapto, halogeno, trifluoromethyl, nitro and amine groups; and A represents a lower alkylene or lower alkenylene radical that is unsubstituted or substituted by one or more of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkenyloxy, lower alkyl - mercapto, halogeno and oxo groups; provided that R₁ represents a cycloalkyl or cycloalkyl - lower alkyl group, and/or A represents lower alkenylene radical which may be substituted as defined above; and the functional acid and amino derivatives, as hereinafter defined, and physiologically tolerable salts, thereof.

The term "lower", referred to above and

hereinafter in connection with an organic radical, group or compound denotes such radical, group or compound as having up to 7, preferably up to 4, carbon atoms.

A lower alkyl radical represented by R₂ is, for example, a methyl, ethyl *n* - propyl, *iso* - propyl, *n* - butyl, isobutyl, *sec.* butyl, *tert.* - butyl, *n* - pentyl, *isopentyl*, *n* - hexyl, *iso* - hexyl, *n* - heptyl or *isohexyl* group.

A cycloalkyl radical represented by R₁ has preferably 3 to 7 ring members; such as radical. A cycloalkyl - lower alkyl radical *n* - butyl, cyclopentyl, cyclohexyl, or cycloheptyl radical. A cycloalkyl - lower alkyl radical represented by R₂ is one of the above-mentioned lower alkyl groups, having preferably up to 4 carbon atoms and attached to any available position, preferably to the terminal carbon atom, of one of the above mentioned cycloalkyl radicals. Such a group is, for example, a cyclopropylmethyl or 2 - cyclopentylethyl group.

The phenylene radical represented by Ph, which carries the tertiary amino group of the

formula A N — in the 2-, or preferably the

3-, and above all in the 4-position, may be unsubstituted, or may be substituted in the remaining positions by one or more, preferably one or two, of the same or different substituents. Such a substituent is a lower alkyl group (e.g. a methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl, or isobutyl group), a free hydroxy or mercapto group, a lower alkoxy group (e.g. a methoxy, ethoxy, *n* - propyloxy, *isopropoxy*, *n* - butyloxy, or isobutyl - oxy group), a lower alkyl - mercapto group (e.g. a methylmercapto or ethylmercapto group), a halogeno group (e.g. a fluoro, chloro

or bromo group), or a trifluoromethyl, nitro, or amino group, preferably a di-lower alkyl-amino group (e.g. a dimethylamino, N-methyl - N - ethylamino, diethylamino, di-
 5 *n* - propylamino, diisopropylamino, di - *n* - butylamino or di - isobutylamino group) or another group of the formula $\text{A}-\text{N}-$, A having the above meaning, or a lower alkanoyl - amino group (e.g. an acetylamino or pivaloyl-
 10 amino group).
 More particularly, the phenylene radical represented by pH is primarily 1,3- or 1,4 - phenylene, a (lower alkyl) - 1,3 - phenylene or 1,4 - phenylene, a (lower alkoxy) - 1,3 -
 15 phenylene or 1,4 - phenylene, a (mono- or di - halogeno) - 1,3 - phenylene or 1,4 - phenylene, a (trifluoromethyl) - 1,3 - phenylene or 1,4 - phenylene, an (amino) -
 20 1,3 - phenylene or 1,4 - phenylene, a (di - lower alkylamino) - 1,3 - phenylene or 1,4 - phenylene or an $\text{A}-\text{N}-$ 1,3 - phenylene or 1,4 - phenylene.

The group of the formula $\text{A}-\text{N}-$ is a monocyclic lower alkylene - amino or lower
 25 alkenylene - amino group [i.e. an N - aza - cycloalk(en)yl radical], e.g. an ethyleneamino, azetidino, pyrrolidino, 3 - pyrrolino, piper-
 30 idino, 3 - piperidino, 1,4 - pentyleneamino, 2,5- or 1,6 - hexyleneamino or 2,6- or 1,7- heptyleneamino group. The above alkylene- and alkenylene- amino groups may be unsubstituted or substituted by one or more substituents, which may be the same or different
 35 selected from lower alkyl, free hydroxyl, free mercapto, lower alkoxy, lower alkanoyloxy, lower alkyl - mercapto, halogeno, and oxo groups.

A functional derivative of an acid of formula I is an ester, for example a lower
 40 alkyl ester, a hydroxy - lower alkyl ester, a lower alkoxy - lower alkyl ester or a *tert* - amino - lower alkyl ester, in which the tertiary amino group is, for example, a di - lower alkyl - amino group (e.g. a dimethyl -
 45 amino or diethylamino group) or a lower alkylene - amino group (e.g. a pyrrolidino or piperidino group).

In the above esterifying moieties the groups are primarily those mentioned above; in case
 50 one of them contains hetero atoms, these are separated from each other and from the oxygen atom of the carboxy group by at least 2, preferably 2 or 3, carbon atoms.

Another functional derivative of an acid of formula I is an optionally substituted amide or thioamide, e.g. a mono - lower alkyl- or
 55 di - lower alkyl - amide, a monocyclic lower alkylene - amide or monooxa - lower alkylene- amide, or a corresponding thioamide, an op-

tionally substituted hydroxyamide (i.e. a hydroxamic acid), a nitrile, or an ammonium or metal salt.

A functional amino derivative is an N - oxide, a lower alkyl or phenyl - lower alkyl quaternary ammonium compound or an acid
 60 addition salt.

The compounds of the invention possess valuable pharmacological properties. For example, they exhibit antiinflammatory effects, which can be demonstrated in animal tests, using advantageously mammals, (e.g. rats) as test objects. According to the test method described by Winter *et al*, *Proc. Soc. Expt. Biol. & Med.* Vol. 111, p. 544 (1962), the compounds of this invention are administered, in the form of aqueous solutions or suspensions, by stomach tube to mature male and female rats.

About one hour later, a 1% aqueous suspension of carrageenin is injected into the rat's left hind paw. After 3 hours the volume and/or weight of the edematous left hind paw are compared with that of the right hand paw. The difference between the two extremities is compared with the one measured in untreated control animals; the comparison is used to express the anti-inflammatory effects of the test substances. The compounds of the invention are, therefore, useful anti-inflammatory agents in the treatment or management of arthritic and dermatopathologic conditions. They are also useful as intermediates in the preparation of other valuable products, preferably of pharmacologically active compounds.

Preferred compounds of the invention are, particularly in view of their anti-inflammatory properties, those of formula I, in which R₁ represents a hydrogen atom, a lower alkyl group, a 3 to 7 ring-membered cycloalkyl group, or a cycloalkyl - lower alkyl group in which the cycloaliphatic residue has 3 to 7 ring members: Ph represents a phenylene radical that is unsubstituted or substituted by one or two substituents, which may be the same or different, selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkyl-mercapto, trifluoromethyl, nitro, amino, di - lower alkyl - amino and lower alkanoyl - amino groups, halogen atoms, and groups of
 100 105 110

the formula $\text{A}-\text{N}-$, where A has the follow-

ing meaning; and A represents a monocyclic lower alkylene group or a lower alkenylene group, or the said alkylene or alkenylene radicals substituted by one or two substituents selected from hydroxy, mercapto, lower alkoxy, lower alkyl - mercapto, lower alkanoyloxy and oxo groups and halogen atoms; provided that R₁ represents a 3 to 7 ring-membered cycloalkyl group or a cycloalkyl - lower alkyl group, in which the cycloaliphatic radical contains 3 to 7 ring members, and/or
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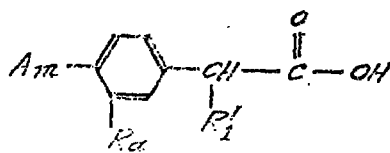
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A represents a lower alkenylene group which may be substituted as defined above; as well as their lower alkyl, hydroxy - lower alkyl, lower alkoxy - lower alkyl, di - lower alkyl - amino - lower alkyl and lower alkenylene - amino - lower alkyl esters; their amides, mono - lower alkyl- and di - lower alkyl - amides, lower alkenylene - amides, morpholides, thioamides, mono - lower alkyl- and di - lower alkyl - thioamides, lower alkenylene - thio - amides, and thiomorpholides; as well as hydroxamic acids, N - oxides, lower alkyl or phenyl - lower alkyl quaternary ammonium compounds and physiologically tolerable salts of these compounds.

Particularly useful compounds of the invention, especially in view of their anti-inflammatory effects, are the compounds of formula I, in which R₁ represents a hydrogen atom, a lower alkyl group, or a 3 to 7 ring-membered cycloalkyl group; Ph represents a 1,3- or 1,4 - phenylene radical that is unsubstituted or substituted by a lower alkyl, lower alkoxy, trifluoromethyl, di - lower alkyl - amino or lower alkenylene - amino group, or by one or two halogen atoms; and

the group of the formula $\text{A} \text{---} \text{N} \text{---}$ is lower alkenylene - amino, hydroxy - lower alkenylene - amino or lower alkenylene - amino group; provided that R₁ represents a 3 to 7 ring-membered cycloalkyl group, and/or $\text{A} \text{---} \text{N} \text{---}$ represents a lower alkenylene - amino group; and the lower alkyl esters, amides, mono - lower alkyl- and di - lower alkyl - amides, ammonium salts, alkali metal and alkaline earth metal salts and physiologically tolerable acid addition salts, thereof.

Preferred compounds of the invention, primarily in view of their anti-inflammatory effects, are those of the formula



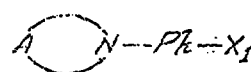
(Ia)

in which Am represents a lower alkenylene - amino group, R₁' represents an unsubstituted cycloalkyl group having 3 to 6 ring members, and R represents a hydrogen atom, or a lower alkyl, lower alkoxy, halogeno, or trifluoromethyl group; and the lower alkyl esters, ammonium salts, alkali metal salts and physiologically tolerable acid addition salts, thereof.

Especially valuable compounds of the invention, particularly in view of their pharma-

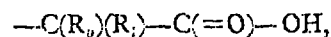
cological properties, are compounds of the formula Ia, in which Am represents a piperidino, pyrrolidino, N - hexamethyleneamine or N - heptamethyleneamino group, R₁' represents a cyclopropyl group and R₁ represents a hydrogen atom or a chloro group; and the methyl and ethyl esters, ammonium salts, alkali metal salts and physiologically tolerable acid addition salts, thereof

The compounds of this invention may be obtained according to methods known *per se*, (a) by reacting a compound of the formula



(II)

in which A has the meaning given for formula I and X₁ represents a grouping of the formula $\text{---CH(R}_1\text{)---Y}_1$, in which Y₁ represents an alkali metal atom, a halogeno - magnesium group or a reactive, esterified or etherified hydroxyl group, with a reactive derivative of carbonic acid or of formic acid, not more than one of the reactants containing a metal atom; or (b) oxidizing in a compound of the formula II in which X₁ represents a grouping of the formula $\text{---CH(R}_1\text{)---Y}_2$, in which Y₂ represents a hydroxymethyl or boryl - methyl group, a formyl group or a 1 - lower alkenyl or lower alkenoyl group, the group represented by Y₂; or (c) reacting a compound of the formula II in which X₁ represents a grouping of the formula $\text{---CH(R}_1\text{)---Y}_2$, in which Y₂ represents an ammonium group, with a metal cyanide; or (d) decarbonylating a compound of the formula II in which X₁ represents a grouping of the formula $\text{---CH(R}_1\text{)---Y}_2$, in which Y₂ represents a carboxycarbonyl group; or (e) reacting a compound of the formula II in which X₁ represents an acetyl group, with sulfur in the presence of ammonia or a primary or secondary amine; or (f) reacting a compound of the formula II in which X₁ represents a halogeno - carbonyl group, with an R₁ - diazo compound and rearranging it by hydrolysis, alcoholysis, ammonolysis or aminolysis; or (g) reacting a compound of the formula II in which X₁ represents a 1 - lower alkenyl group, with carbon monoxide and water under acidic conditions; or (h) decarboxylating a compound of the formula II in which X₁ represents a free or functionally converted grouping of the formula



in which R₂ represents a carboxy group; or (i) converting in a compound of the formula II, in which X₁ represents a free or functionally converted grouping of the formula

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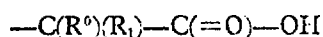
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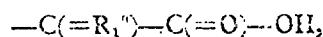
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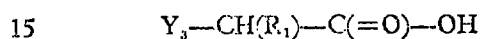
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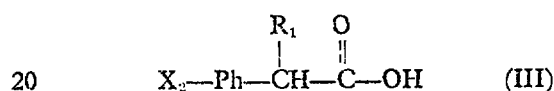
or of the formula



- 5 in which R^0 represents a free or reactive esterified hydroxyl group, and R_1'' represents a lower alkylidene or cycloalkylidene group, the group represented by R^0 into a hydrogen atom or the group represented by R_1'' into a group represented by R_1 , by reduction; or (k) reacting a compound of the formula II in which X_1 represents a hydrogen atom or a metal atom or a metal grouping, with a reactive ester of a glycolic acid compound of the formula



or a functional acid derivative thereof, in which Y_3 represents a reactive, esterified hydroxyl group; or (m) reacting a compound of the formula



or a functional acid derivative thereof, in which X_2 represents a reactive esterified hydroxyl group, with a secondary amine of the formula $A-N-H$ or an alkali metal

- 25 derivative thereof, or (n) reacting a compound of the formula III in which X_2 represents a primary amino group, with a reactive esterified glycol of the formula $HO-A-OH$; and, if desired, converting a resulting ester, amide, thioamide or nitrile into the corresponding free acid, by hydrolysis; and, if desired, converting, in a resulting compound with a free carboxyl group, the latter into an esterified carboxyl group; and, if desired, converting a resulting compound with a free carboxyl group into an acid halide and reacting the latter with an alcohol, ammonia or an amine; and, if desired, metallizing a resulting ester, salt or nitrile of a compound of the formula I in which R_1 represents a hydrogen atom, in the α -position, and reacting it with a reactive ester of an alcohol of the formula R_2-OH ; and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the corresponding free compound; and/or, if desired, resolving a resulting mixture of isomers into the separate isomers.

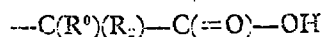
- 30 In method (a), an alkali metal represented by Y is, for example, lithium, sodium or potassium, and a reactive etherified or esterified hydroxy group is, for example, a lower alkoxy group or a hydroxy group esterified by a strong mineral acid, particularly by a hydrohalic acid, (e.g. hydrochloric or hydro-

bromic acid), by a sulfuric acid or by an organic acid, for example a lower alkane sulfonic or benzene sulfonic, e.g. methane sulfonic, ethane sulfonic or *p*-toluene sulfonic acid. The metal or Grignard compound can be reacted with any suitable metal free carbonic or formic acid derivative, advantageously with carbon dioxide or carbon disulphide, but alternatively with a carbonate, e.g. diethyl carbonate or diethyl thiocarbonate, with a halogeno-formate, e.g. ethyl, *tert*.-butyl, allyl, 2-methoxyethyl, 3-chloropropyl, phenyl or benzyl chloroformate, with a cyanogen halide, e.g. cyanogen bromide, or with a carbamoyl halide, e.g. diethylcarbamoyl chloride. A reactive esterified hydroxy compound is advantageously reacted with a metal cyanide, for example an alkali metal, e.g. sodium or potassium, cyanide.

An ammonium group represented by Y_2 , in method (c), e.g. the trimethylenammonium group, can be replaced by a cyano group upon reacting the starting material with an alkali metal cyanide, e.g. potassium cyanide. A hydroxy-methyl or borylmethyl group, a formyl group, a 1-lower alkenyl or lower alkenoyl group represented by Y_2 , in method (b), can be converted into a carboxy group according to standard oxidation procedures, for example, with the use of hydrogen peroxide, or a heavy metal salt or oxide, e.g. an alkali metal chromate or permanganate, with a chromic or cupric salt, e.g. a halide or sulfate, or with a mercuric, manganese or silver oxide, in an acidic or an alkaline medium, depending on the type of reagent used. Decarbonylation of a carboxycarbonyl group represented by Y_1 , in method (d), is preferably carried out by pyrolysis, advantageously in the presence of copper powder.

An acetyl group represented by X_1 (method (e)) is oxidized according to the Willgerodt-Kindler reaction by treatment with sulphur in the presence of ammonia or of a primary or secondary amine, the corresponding thiocarbamylmethyl grouping being formed. A starting material, in which X represents a halogeno-carbonyl group, for example, a chloro-carbonyl group, may be treated according to the Arndt-Eistert reaction with an R_1 -diazo compound (method (f)); the resulting diazoketone may be rearranged by hydrolysis, alcoholysis, ammonolysis or aminolysis. A starting material with a 1-lower alkenyl group represented by X_2 , may be reacted, according to method (g), with carbon monoxide and water under acidic conditions, for example, in the presence of sulfuric acid.

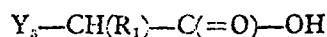
A reactive esterified hydroxyl group represented by R'' , in method (j), in a free or functionally converted grouping of the formula



is, for example, a halogen atom, R_2 , R^0 and

R_1^o and R_2^o may be removed or converted according to standard decarboxylation or reduction methods. Pyrolysis, preferably under acidic conditions, may be advantageously used as a decarboxylation method in method (h), whereas reduction, in method (i), may be carried out, for example, with catalytically activated or nascent hydrogen (e.g. hydrogen in the presence of a nickel, palladium or platinum catalyst); the reduction of an α -hydroxyacid starting material may alternatively be carried out with phosphorus and iodine, hydriodic acid or stannous chloride.

In method (k), a metal atom represented by X_1 is, for example, an alkali metal atom, e.g. lithium, and a metal grouping is, for example, a halogeno - magnesium grouping. In the glycolic acid compound of the formula



or a functional derivative thereof, e.g. an ester, an amide or a nitrile, a reactive esterified hydroxy group represented by Y_2 is, for example, a halogen atom, e.g. a chlorine or bromine atom, or an organic sulphonyloxy group, e.g. a benzenesulphonyloxy or toluenesulphonyloxy group. The reaction involving a starting material, wherein X_1 represents a hydrogen atom, may be performed in the presence of a suitable Lewis acid, e.g. aluminium chloride.

A reactive esterified hydroxy group represented by X_2 in a starting material of the formula III (method (m)) is, for example, a hydroxy group esterified by a strong acid, e.g. a halogen atom, advantageously a fluorine atom, which may be replaced by the group

of the formula $\overset{\text{A}}{\text{N}}-$ by reacting the starting material containing such a group with a secondary amine of the formula $\overset{\text{A}}{\text{N}}-\text{H}$

or with an alkali metal derivative thereof.

A reactive esterified glycol of the formula $\text{HO}-\text{A}-\text{OH}$, in method (n), is, for example, a lower alkylene, monoaza - lower alkylene, monooxa - lower alkylene or monothia - lower alkylene dihalide, e.g. a dichloride or dibromide, or a reactive functional acid derivative, e.g. a halide, anhydride or lactone, corresponding to such a glycol.

The compounds of the invention so obtained can be converted into each other according to methods known *per se*. Thus, a resulting free acid may be esterified, for example, by treatment with the corresponding alcohol in the presence of a strong acid, e.g. hydrochloric, sulphuric, benzenesulphonic or *p* - toluene sulphonic acid, or with a diazo compound, or converted into the acid halide, for example, by treatment with a thionyl halide, e.g. thionyl chloride, or with a phosphorus halide, e.g.

phosphorus tribromide, or with a phosphorus oxyhalide, e.g. phosphorus oxychloride. A resulting ester may be hydrolysed to the free acid or trans-esterified into another ester by treatment with an alcohol, for example, in the presence of an acidic or alkaline agent, for example a mineral acid or a complex heavy metal acid, as well as an alkali metal carbonate or alcoholate; upon treatment with ammonia or a suitable amine an ester may be converted into an amide.

A resulting acid halide may be treated with an alcohol, as well as with ammonia or an amine, and a resulting metal or ammonium salt with an aliphatic or araliphatic halide e.g. chloride or bromide, or with an aliphatic or araliphatic chlorosulphite, or thionyl halide, e.g. thionyl chloride, or with phosphorus pentoxide, phosphorus pentasulphide, or a phosphorus halide, e.g. phosphorus pentachloride, or with a phosphorus oxyhalide, e.g. phosphorus oxychloride, or another acyl halide, e.g. chloride, in order to form the corresponding ester, halide, anhydride, amide, thioamide or nitrile, depending on the type of starting material and reagent used.

A resulting amide or thioamide (products of the Wilgerodt-Kindler reaction) can be hydrolyzed under acidic or alkaline conditions, e.g. by treatment with an aqueous mineral acid and/or carboxylic acid, or with an alkali metal hydroxide, or can be alcoholized, transaminated or desulphurized, e.g. by treatment with mercuric oxide or an alkyl halide, followed by hydrolysis. A resulting nitrile can be hydrolyzed or alcoholized, e.g. by treatment with a concentrated aqueous or alcoholic acid or with an alkali metal hydroxide, or with alkaline hydrogen peroxide.

A resulting ester, salt or nitrile of a compound of the formula I in which R_1 represents a hydrogen atom, can be metallized in the α - position, for example, by treatment with an alkali metal organic compound, e.g. phenyl lithium, or triphenylmethyl sodium, or sodium amide or alcoholate, and then be reacted with a reactive ester of an alcohol of the formula $R_1-\text{OH}$, and thus be substituted in the α - position.

A resulting compound containing a primary or secondary amino group, can be reacted with a reactive ester of a corresponding alcohol, for example, one mentioned above, or can be acylated, for example, with a reactive functional derivative of a corresponding acid, for example a halide, e.g. a chloride, or an anhydride thereof. A resulting acyl derivative may be split, for example, by treatment with the use of an acidic or alkaline hydrolyzing agent, or a phthaloyl - amino compound by hydrazinolysis.

A resulting compound may also be halogenated or nitrated in the aromatic moiety represented by Ph; nitration being effected, for example, by treatment with nitric acid

and/or a nitrate salt under acidic conditions. A nitro group may be reduced to an amino group; these may be converted, for example, via a diazonium salt, e.g. a diazonium halide, for example, in the presence of a copper - I - halides, e.g. into a halogen atom. In a compound with a phenolic hydroxy or mercapto group, these groups may be etherified, e.g. by using the corresponding alkali metal phenolate and lower alkyl halide, e.g. chloride or bromide, sulphate or sulphonate. A resulting phenol ether may be hydrolyzed, for example, with hydrobromic and acetic acid, or with pyridine hydrochloride.

A resulting free acid can be converted into its salts by conventional methods, for example, by reaction with an approximately stoichiometric amount of a suitable salt-forming reagent, for example ammonia, an amine or an alkali metal or alkaline earth metal hydroxide, carbonate or hydrogen carbonate. A salt of this type can be reconverted into the free acid by treatment with an acid, e.g. hydrochloric, sulphuric or acetic acid until the proper pH has been reached.

A resulting compound can be converted into an acid addition salt, for example, by reaction with an inorganic or organic acid, or with a corresponding anion exchange preparation, and isolation of the resulting salt. An acid addition salt may be converted into the free compound by treatment with a base, e.g. an alkali metal hydroxide, ammonia or a hydroxyl ion exchange preparation. A physiologically tolerable acid addition salt is, for example, are with an inorganic acid, e.g. hydrochloric, hydrobromic, sulphuric, phosphoric, nitric or perchloric acid, one with an organic acid, for example a carboxylic or sulphonic acid, e.g. formic acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic phenylacetic, benzoic, 4 - aminobenzoic, anthranilic, 4 - hydroxy - benzoic, salicylic, aminosalicylic, embonic or nicotinic acid, as well as methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic, benzenesulphonic, halogenbenzenesulphonic, toluenesulphonic, naphthalenesulphonic, sulphanilic or cyclohexylsulphamic acid, furthermore, methionine, tryptophan, lysine or arginine.

These or other salts, for example, the picrates, are also for purification purposes; thus, a free compound is converted into a salt, the latter is separated from the crude mixture and the free compound is then liberated from the isolated salt. In view of the close relationship between the free compounds and their salts, reference in this context to a free compound or a salt is also intended to be a reference to the corresponding salt and free compound, respectively, provided such is possible or appropriate under the circumstances.

A resulting mixture of isomers can be separated into the single isomers by known methods e.g. by fractional distillation or crystallization and/or chromatography. A racemic product can likewise be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g. by fractional crystallization of a mixture of the diastereoisomeric salts with *d* - or *l* - tartaric acid, or with *d* - α - phenyl - ethyl - amine or *d* - α - (1 - naphthyl) - ethyl - amine or *l* - cinchonidine, if desired, followed by liberation of the free antipodes from the salt.

The above reactions may be carried out according to standard methods, e.g. in the presence or absence of diluents, preferably those which are inert towards the reagents and/or are capable of dissolving them, if necessary, in the presence of catalysts, condensing or neutralizing agents, in an inert atmosphere, under cooling or heating and/or under increased pressure.

The invention also comprises any modification of the above process in which starting materials are formed under the reaction conditions or are used in the form of salts or reactive derivatives.

Those starting materials are preferably used which lead to compounds previously indicated as representing the preferred embodiments of the invention.

The starting materials used in the above procedure are known or, if new, may be prepared according to methods known *per se*. For example, a starting material of the formula II may be prepared from a compound of the formula A N—Ph—II according to the

Friedel-Crafts reaction, e.g. by treatment with a halide, e.g. chloride, of an acid of the formula R₁—C(=O)—OH in the presence of a suitable Lewis acid, e.g. aluminium chloride hydrogen chloride and formaldehyde, or phosgene and aluminium chloride. The resulting ketone or acyl halide is either used as such in the above-mentioned Willgerodt-Kindler or Arndt-Eistert reaction, or the ketone is reduced to the corresponding alcohol, advantageously by using an R₁-Grignard compound or sodium borohydride. This alcohol may also be obtained by reacting a Grignard compound having the residue of the formula

A N—Ph— with an aldehyde of the formula R₁—CHO.

The resulting alcohol can be reactive esterified, for example, with a thionyl halide, (e.g. a chloride), or an organic sulphonyl halide, (e.g. a chloride), or etherified, for example, by treatment with a lower alkanol in the presence of a suitable mineral acid, (e.g. with methanol or ethanol in the presence of

sulfur may an a ether treat or a comp cont A 10 sent an oxal the

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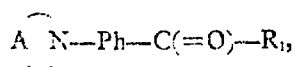
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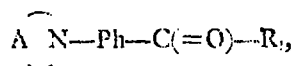
sulfuric acid); if desired, a resulting ester may be converted into an ether, e.g. by using an alkali metal lower alkoxide. A resulting ether or ester may be metallized, e.g. by treatment with magnesium, zinc, mercury and/or an alkali metal, and, if desired, a Grignard compound, in order to form a starting material containing a group represented by Y_1 .

A starting material with a group represented by Y_2 may be obtained by reacting an above metal derivative with a formyl or oxalyl halide, e.g. a chloride, furthermore by the reaction of a compound having the formula



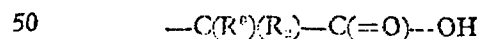
with an halogeno - magnesium reagent, followed by dehydration of a resulting alcohol, for example, by treatment with sulphuric or acetic acid and/or acetic acid anhydride; a resulting methylene compound may then be reacted with a borane compound or with a diluted mineral acid, respectively, and, if desired, a trace of a peroxide, e.g. benzoyl peroxide, in order to yield a desired hydroxy-methyl or borylmethyl compound.

A starting material of the formula II, in which Y_2 represents a formyl group, can be obtained from a ketone of the formula

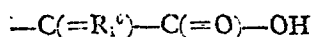


by reaction with dimethylsulphonium - methylide or dimethyl - oxysulphonium - methylide (generated from the corresponding trimethylsulphonium salt) and rearrangement of the resulting ethyleneoxide compound to the corresponding aldehyde by the action of a Lewis acid, e.g. *p* - toluene sulphonie acid or boron trifluoride. This aldehyde may also be obtained according to the Darzens condensation by reacting the above mentioned ketone with an α - halogeno - alkanolic or α - halogeno - alkenolic acid esters in the presence of an alcoholate, for example an alkali metal lower alkanolate, e.g. potassium *tert* - butoxide, saponifying the resulting glycidic acid ester, and rearranging and decarboxylating the free acid, advantageously in an acidic medium, e.g. sulphuric acid.

Finally, a starting material of the formula II, containing the free or functionally converted grouping of the formula



or the formula



can be obtained according to the Friedel-

Crafts reaction by using a compound of the formula $\text{A} \begin{pmatrix} \text{N} \end{pmatrix} \text{—Ph—H}$ and an oxalyl

halide, e.g. a chloride. The resulting phenylglyoxylic acid ester may be reduced upon treatment with an R_1 -Grignard compound, followed, if desired, by dehydration. It may also be obtained according to the Ando synthesis by addition of a mesoxalic acid ester to the above mentioned *tert* - aniline compound in the presence of stannic chloride; the resulting adduct can then either be hydrogenated, the malonic acid ester formed may be metallized and reacted with a reactive ester of a compound of the formula $R_1\text{—OH}$, or saponified and decarboxylated. The corresponding nitrile can also be obtained from the above Friedel-Crafts ketone according to the cyanohydrin synthesis; if desired, the product may be hydrolyzed and/or dehydrated.

A starting material of the formula III may be prepared according to the above procedure using a starting material of the formula II, in which the *tert* - amino group of the

formula $\text{A} \begin{pmatrix} \text{N} \end{pmatrix}$ is replaced by a grouping

X_2 capable of being converted into the latter.

An intermediates or starting material obtained according to the above procedure, can also be converted into another intermediate or starting material in a manner analogous to the reactions shown above for the final product.

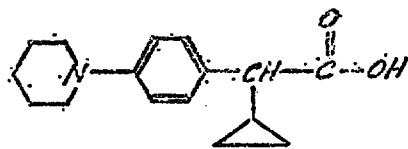
The pharmacologically active compound of the invention can be used, for example, for the manufacture of pharmaceutical preparations containing them in conjunction or admixture with an inorganic or organic, solid or liquid pharmaceutically acceptable carrier, suitable for enteral or parenteral administration. Such carrier materials are substances that do not react with the compounds of the invention, for example, water, gelatine, sugars, e.g. lactose, glucose or sucrose, starches, e.g. corn starch, wheat starch, rice starch, or arrowroot, stearic acid or salts thereof, e.g. magnesium or calcium stearate, talc, vegetable fats or oils, gums, alginic acid, benzyl alcohols, glycols or polyglycols and other known excipients. The preparations may be in solid form, e.g. as tablets, dragees, capsules, or suppositories, or in liquid form, e.g. as solutions, suspensions or emulsions. They may be sterilized and/or contain auxiliary agents, such as preserving, stabilizing, wetting or emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers. They may further contain other therapeutically valuable substances. Said pharmaceutical preparations are prepared by conventional methods and contain about 0.1% to about 75%, more particularly about 1% to about 50%, of the active ingredient. They are also

included within the scope of the present invention.

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

EXAMPLE 1

A mixture of 14.9 g of silver nitrate, 8.8 g of sodium hydroxide and 88 ml of water, is treated at room temperature and while stirring with 10.5 g of α - cyclopropyl - α - (4 - piperidino - phenyl) - acetaldehyde and stirred for 13 hours. The reaction mixture is filtered with the aid of infusorial earth; the filtrate is neutralized with hydrochloric acid and lyophilized. The residue is triturated repeatedly with small portions of methanol and filtered. The methanol solution is evaporated; the residue is taken up in 10 ml of acetonitrile and 12 ml of bis - (trimethylsilyl) - trifluoroacetic acid amide. The solution is filtered, the filtrate is evaporated and the resulting trimethylsilyl ester is slowly distilled in a short-path distilling apparatus at a pressure of 0.02 mm Hg. The fraction, obtained at the bath temperature of 120°, is dissolved in 10 ml of aqueous methanol; the solution is allowed to stand for 20 minutes and evaporated to yield α - cyclopropyl - α - (4 - piperidino - phenyl) - acetic acid of the formula



which melts at 149—151° after recrystallization from methanol.

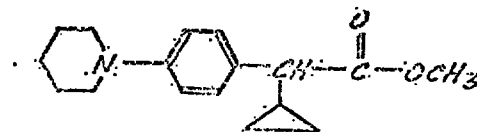
The starting material is prepared as follows: The mixture of 5.7 g of sodium hydride and 120 ml of anhydrous dimethylsulphoxide is stirred for one hour at 60—70° under a nitrogen atmosphere. The mixture is cooled, diluted with 120 ml of dry tetrahydrofuran and treated with 49.1 g of trimethylsulphonium iodide in 195 ml of dimethylsulphoxide, which is added as rapidly as possible while keeping the temperature at about -10°. After stirring for one minute, a solution of 22.9 g of 4 - piperidinophenyl cyclopropyl ketone in 195 ml of tetrahydrofuran is added, and the mixture is stirred for 5 to 10 minutes, then filtered through a sintered glass filter. The filtrate is diluted with water (three times the volume) and extracted with ether. The organic extract is washed eight times with water and once with a saturated aqueous sodium chloride solution, dried and evaporated under reduced pressure to yield 1 - cyclopropyl - 1 - (4 - piperidino - phenyl) - ethyleneoxide.

A solution of 1.9 g of anhydrous p -

toluenesulphonic acid in 600 ml of benzene is treated with 23 g of 1 - cyclopropyl - 1 - (4 - piperidino - phenyl) - ethylene oxide; the mixture is refluxed for 18 hours, then cooled, washed with an aqueous sodium hydrogen carbonate solution and water, dried and evaporated under reduced pressure to yield the α - cyclopropyl - α - (4 - piperidino - phenyl) - acetaldehyde.

EXAMPLE 2

A mixture of 1 g of α - cyclopropyl - α - (4 - piperidino - phenyl) - acetic acid and 10 ml of a saturated solution of hydrogen chloride in methanol is heated on the steam bath and slowly evaporated. The residue is taken up in chloroform; the organic solution is washed with a saturated aqueous sodium bicarbonate solution and water, dried and evaporated. The residue is distilled in a short-path distillation apparatus; the fraction boiling at a bath temperature of 118° and a pressure of 0.1 mm Hg represents methyl α - cyclopropyl - α - (4 - piperidino - phenyl) - acetate of the formula



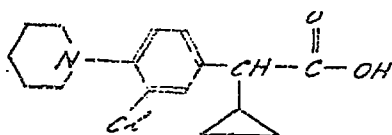
EXAMPLE 3

A solution of 24 g of α - cyclopropyl - α - (4 - piperidino - phenyl) - acetaldehyde in 200 ml of acetone is slowly added while stirring and at a temperature of -15 to -20° to a chromic acid solution, prepared from 10 g of chromium trioxide and 16 g of concentrated sulphuric acid, made up with water to a volume of 100 ml; stirring is continued for 2 hours. After standing for 16 hours at room temperature, the mixture is diluted with 600 ml of water and extracted ten times with 100 ml portions of chloroform. The organic extract is dried and evaporated, and the residue is taken up in 36 ml of bis - (trimethylsilyl) - trifluoroacetic acid amide and 20 ml of acetonitrile. The mixture is evaporated; the residue is distilled in a high vacuum and the distillate is taken up in aqueous methanol. After standing for 16 hours, the solution is evaporated and the residue is recrystallized from methanol to yield α - cyclopropyl - α - (4 - piperidino - phenyl) - acetic acid, m.p. 148—150°C.

EXAMPLE 4

To the solution of 6 g of α - cyclopropyl - α - (4 - piperidino - phenyl) - acetic acid hydrochloride in 55 ml of acetic acid, about 200 ml of acetic acid saturated with chlorine are added dropwise while stirring; the course of the chlorination is followed by thin layer

chromatography. Upon completing the reaction, the mixture is evaporated under reduced pressure; the residue is taken up in 100 ml of water and 50 ml of ethanol and the solution is adjusted to pH 5.5 with 10% aqueous ammonia. The precipitate formed in the cold is recrystallized once from cyclohexane and once from a mixture of *n*-hexane and cyclohexane, to yield α - (3 - chloro - 4 - piperidino - phenyl) - α - cyclopropyl - acetic acid of the formula

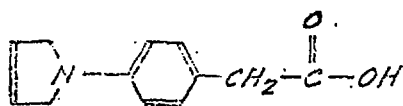


melting at 129—131°.

The starting material is prepared as follows: To the solution of 5.5 g of α - cyclopropyl - α - (4 - piperidino - phenyl) - acetic acid in 15 ml of chloroform and 25 ml of ether, a saturated solution of hydrogen chloride in ether is added until the precipitate is complete. The mixture is filtered and the residue is washed with ether, to yield the corresponding hydrochloride, m.p. 193—195° (with decomposition).

EXAMPLE 5

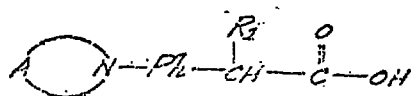
A mixture of 10.8 g of ethyl 4 - amino - phenylacetate hydrochloride, 32.4 g of 1,4 - dibromo - 2 - butene, 84 g of sodium bicarbonate and 500 ml of dimethylformamide is refluxed for 6 hours while stirring, then filtered hot. The filtrate is evaporated under reduced pressure; the residue is taken up in 150 ml of 25% aqueous sodium hydroxide and the mixture refluxed for 1 hour, cooled and washed with ether, then adjusted to pH 5 with hydrochloric acid and extracted with ether. The organic extract is dried, filtered and evaporated, to yield α - (4 - Δ^2 - pyrrolidino - phenyl) - acetic acid of the formula



m.p. 162—165°.

WHAT WE CLAIM IS:—

1. A compound of the formula



(I)

in which R_1 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group or a cycloalkyl - lower alkyl group; Ph represents a phenylene radical or a phenylene radical substituted by one or more of the same or different substituents selected from lower alkyl, free hydroxy, free mercapto, lower alkoxy, lower alkyl - mercapto, halogeno, trifluoro - methyl, nitro and amino groups; and A represents a lower alkylene or lower alkenylene radical that is unsubstituted or substituted by one or more of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkanoyloxy, lower alkyl - mercapto, halogeno and oxo groups; provided that R_2 represents a cycloalkyl or cycloalkyl - lower alkyl group and/or A represents a lower alkenylene radical which may be substituted as defined above.

2. A functional acid or amino derivative, as hereinbefore defined, of a compound claimed in claim 1.

3. A physiologically tolerable salt of a compound claimed in claim 1 or 2.

4. A compound of formula I as shown in claim 1, in which Ph has the meaning given in claim 1, R_1 represents a 3 to 7 membered cycloalkyl group, and A represents a lower alkylene radical.

5. A functional acid or amino derivative, as hereinbefore defined, of a compound claimed in claim 4.

6. A physiologically tolerable salt of a compound claimed in claim 4 or claim 5.

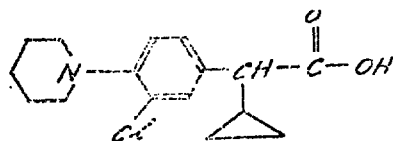
7. A compound of formula I as shown in claim 1, in which R_1 represents a hydrogen atom, a lower alkyl group, a 3 to 7 ring-membered cycloalkyl group, or a cycloalkyl - lower alkyl group in which the cycloaliphatic radical contains 3 to 7 ring members; Ph represents a phenylene radical that is unsubstituted or substituted by one or two of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkyl - mercapto, trifluoromethyl, nitro, amino, di - lower alkyl - amino and lower alkanoyl - amino groups, halogen atoms, and

groups of the formula $\text{A}-\text{N}-$; and A represents

a monocyclic lower alkylene or lower alkenylene group, or a lower alkylene or lower alkenylene group substituted by one or two of the same or different substituents selected from hydroxy, mercapto, lower alkoxy, lower alkyl - mercapto, lower alkanoyloxy and oxo groups and halogen atoms; provided that R_1 represents a 3 to 7 ring-membered cycloalkyl group or a cycloalkyl - lower alkyl group in which the cycloaliphatic radical contains 3 to 7 ring members, and/or A represents a lower alkenylene group which may be substituted as defined above.

8. A lower alkyl, hydroxy - lower alkyl,

chromatography. Upon completing the reaction, the mixture is evaporated under reduced pressure; the residue is taken up in 100 ml of water and 50 ml of ethanol and the solution is adjusted to pH 5.5 with 10% aqueous ammonia. The precipitate formed in the cold is recrystallized once from cyclohexane and once from a mixture of *n*-hexane and cyclohexane, to yield α - (3 - chloro - 4 - piperidino - phenyl) - α - cyclopropyl - acetic acid of the formula

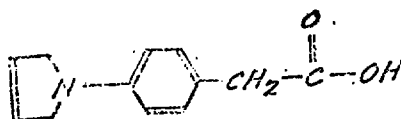


melting at 129—131°.

The starting material is prepared as follows: To the solution of 5.5 g of α - cyclopropyl - α - (4 - piperidino - phenyl) - acetic acid in 15 ml of chloroform and 25 ml of ether, a saturated solution of hydrogen chloride in ether is added until the precipitate is complete. The mixture is filtered and the residue is washed with ether, to yield the corresponding hydrochloride, m.p. 193—195° (with decomposition).

EXAMPLE 5

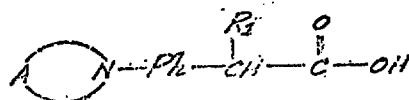
A mixture of 10.8 g of ethyl 4 - amino - phenylacetate hydrochloride, 32.4 g of 1,4 - dibromo - 2 - butene, 84 g of sodium bicarbonate and 500 ml of dimethylformamide is refluxed for 6 hours while stirring, then filtered hot. The filtrate is evaporated under reduced pressure; the residue is taken up in 150 ml of 25% aqueous sodium hydroxide and the mixture refluxed for 1 hour, cooled and washed with ether, then adjusted to pH 5 with hydrochloric acid and extracted with ether. The organic extract is dried, filtered and evaporated, to yield α - (4 - Δ^2 - pyrrolidino - phenyl) - acetic acid of the formula



m.p. 162—165°.

WHAT WE CLAIM IS:—

1. A compound of the formula



in which R_1 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group or a cycloalkyl - lower alkyl group; Ph represents a phenylene radical or a phenylene radical substituted by one or more of the same or different substituents selected from lower alkyl, free hydroxy, free mercapto, lower alkoxy, lower alkyl - mercapto, halogeno, trifluoromethyl, nitro and amino groups; and A represents a lower alkylene or lower alkenylene radical that is unsubstituted or substituted by one or more of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkanoyloxy, lower alkyl - mercapto, halogeno and oxo groups; provided that R_2 represents a cycloalkyl or cycloalkyl - lower alkyl group and/or A represents a lower alkenylene radical which may be substituted as defined above.

2. A functional acid or amino derivative, as hereinbefore defined, of a compound claimed in claim 1.

3. A physiologically tolerable salt of a compound claimed in claim 1 or 2.

4. A compound of formula I as shown in claim 1, in which Ph has the meaning given in claim 1, R_1 represents a 3 to 7 membered cycloalkyl group, and A represents a lower alkylene radical.

5. A functional acid or amino derivative, as hereinbefore defined, of a compound claimed in claim 4.

6. A physiologically tolerable salt of a compound claimed in claim 4 or claim 5.

7. A compound of formula I as shown in claim 1, in which R_1 represents a hydrogen atom, a lower alkyl group, a 3 to 7 ring-membered cycloalkyl group, or a cycloalkyl - lower alkyl group in which the cycloaliphatic radical contains 3 to 7 ring members; Ph represents a phenylene radical that is unsubstituted or substituted by one or two of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkyl - mercapto, trifluoromethyl, nitro, amino, di - lower alkyl - amino and lower alkanoyl - amino groups, halogen atoms, and

groups of the formula $A-N-$; and A represents

a monocyclic lower alkylene or lower alkenylene group, or a lower alkylene or lower alkenylene group substituted by one or two of the same or different substituents selected from hydroxy, mercapto, lower alkoxy, lower alkyl - mercapto, lower alkanoyloxy and oxo groups and halogen atoms; provided that R_1 represents a 3 to 7 ringmembered cycloalkyl group or a cycloalkyl - lower alkyl group in which the cycloaliphatic radical contains 3 to 7 ring members, and/or A represents a lower alkenylene group which may be substituted as defined above.

8. A lower alkyl, hydroxy - lower alkyl,





lower - alkoxy - lower alkyl, di - lower alkyl - amino - lower alkyl or lower alkene - amino - lower alkyl ester; or an amide, mono - lower alkyl- or di - lower alkyl - amide or lower alkylene - amide; or a morpholide, thio - amide, mono - lower alkyl- or di - lower alkyl - thioamide, lower alkylene - thioamide, thiomorpholide, hydroxamic acid, or N - oxide; or a lower alkyl or phenyl - lower alkyl quaternary ammonium compound in which the aromatic radical may contain one or more substituents, which may be the same or different, selected from the substituents given for the group represented by pH in claim 7; or a physiologically tolerable salt; of a compound claimed in claim 7.

9. A compound of the formula I as shown in claim 1, in which R₁ has the meaning given in claim 7. Ph represents a phenylene radical that is unsubstituted or substituted by one or two substituents, which may be the same or different, selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkyl - mercapto, trifluoromethyl, nitro and lower alkanoylamino groups, halogen atoms,

and groups of the formula $\text{A}-\text{N}-$; and A represents a monocyclic lower alkylene or a lower alkenylene group; provided that R₁ represents a 3 to 7 ringmembered cycloalkyl groups or a cycloalkyl - lower alkyl group in which the cycloaliphatic radical contains 3 to 7 ring members, and/or A represents a lower alkenylene group.

10. A lower alkyl, hydroxy - lower alkyl, lower alkoxy - lower alkyl or lower alkylene-amino ester; or an amide, mono - lower alkyl- or di - lower alkyl - amide or lower alkylene-amide; or a thioamide, mono - lower alkyl or di - lower alkyl - thioamide, lower alkylene-thioamide, N - oxide, lower alkyl quaternary ammonium compound, or physiologically tolerable salt; of a compound claimed in claim 9.

11. A compound of the formula I as shown in claim 1, in which R₁ represents a hydrogen atom, a lower alkyl group or a 3 to 7 ring-membered cycloalkyl group, Ph represents a 1,3- or 1,4 - phenylene radical that is unsubstituted or substituted by a lower alkyl, lower alkoxy, trifluoromethyl, di - lower alkyl-amino or lower alkylene - amino group or by 1 or 2 halogen atoms; and the group of the

formula $\text{A}-\text{N}-$ represents a lower alkylene-amino or hydroxy - lower alkylene amino, or a lower alkenylene - amino group; provided that R₁ represents a 3 to 7 ring-membered cycloalkyl group and/or $\text{A}-\text{N}-$ represents a lower alkenylene - amino group.

12. A lower alkyl ester, amide, mono - lower

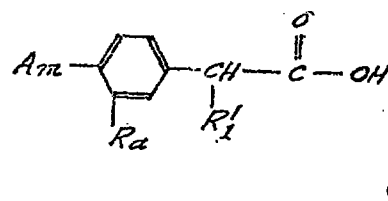
alkyl- or di - lower alkyl - amide, or ammonium, alkali metal or alkaline earth metal salt or a physiologically tolerable acid addition salt, of a compound claimed in claim 11.

13. A compound of formula I as shown in claim 1, in which R₁ represents a 3 to 7 ring-membered cycloalkyl group, Ph represents a 1,4 - phenylene radical that is unsubstituted or substituted by a lower alkyl, lower alkoxy, trifluoromethyl, di - lower alkyl-amino, or lower alkylene - amino group or by 1 or 2 halogen atoms, and the group of the

formula $\text{A}-\text{N}-$ is a lower alkylene - amino group.

14. A lower alkyl ester, an amide, a mono-lower alkyl or di - lower alkyl - amide, or an ammonium, alkali metal or alkaline earth metal salt or a physiologically tolerable acid addition salt, of a compound claimed in claim 13.

15. A compound of the formula



in which Am represents a lower alkylene - amino group, R₁' represents an unsubstituted 3 to 6 ring-membered cycloalkyl group, and R₂ represents a hydrogen atom, or a lower alkyl, lower alkoxy or trifluoromethyl group, or a halogen atom.

16. A lower alkyl ester, an ammonium salt, an alkali metal salt or a physiologically tolerable acid addition salt, of a compound claimed in claim 15.

17. A compound of the formula Ia as shown in claim 15, in which Am represents a piperidino group, R₁' represents a cyclopropyl group and R₂ represents a hydrogen or chlorine atom.

18. An ethyl ester or a physiologically tolerable acid addition salt of a compound claimed in claim 17.

19. A compound of the formula Ia as shown in claim 15, in which Am represents a piperidino, pyrrolidino, N - hexamethylene - amino or N - heptamethylenearmino group and R₁' and R₂ have the meanings given in claim 17.

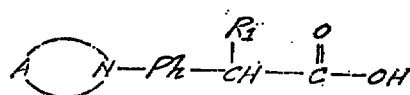
20. A methyl or ethyl ester, an ammonium or alkali metal salt or a physiologically tolerable acid addition salt of a compound claimed in claim 19.

21. α - Cyclopropyl - α - (4 - piper - indino - phenyl) - acetic acid.

22. Methyl α - cyclopropyl - α - (4 - piperidino - phenyl) - acetate.

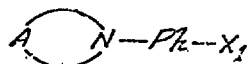


23. A salt of a compound claimed in claim 21 or 22.
24. A physiologically tolerable salt of a compound claimed in claim 21 or 22.
25. A pharmaceutical preparation comprising a compound claimed in any one of claims 4-6 and 13-18 in admixture or conjunction with a pharmaceutically acceptable carrier.
26. A pharmaceutical preparation comprising a compound claimed in claim 9 or 10 in admixture or conjunction with a pharmaceutically acceptable carrier.
27. A pharmaceutical preparation comprising a compound claimed in any one of claims 7, 8, 11, 12, 18-22 and 24 in admixture or conjunction with a pharmaceutically acceptable carrier.
28. A pharmaceutical preparation comprising a compound claimed in any one of claims 1-3 in admixture or conjunction with a pharmaceutically acceptable carrier.
29. A process for the manufacture of a compound of the formula



(I)

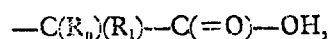
- 25 in which R₁ represents a hydrogen atom, a lower alkyl group, a cycloalkyl group or a cycloalkyl - lower alkyl group, Ph represents a phenylene radical or a phenylene radical substituted by one or more of the same or different substituents selected from lower alkyl, free hydroxy, free mercapto, lower alkoxy, lower alkyl - mercapto, halogeno, trifluoro - methyl, nitro, and amino groups; and A represents a lower alkylene or lower alkenylene that is unsubstituted or substituted by one or more of the same or different substituents selected from lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkanoyloxy, lower alkyl-mercapto, halogeno and oxo groups; provided that R₁ represents a cycloalkyl or cycloalkyl-lower alkyl group, and/or A represents a lower alkenylene radical which may be substituted as defined above; or a functional acid or amino derivative thereof, as hereinbefore defined; which process comprises (a) reacting a compound of the formula



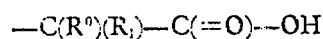
(II)

- in which X₁ represents a grouping of the formula $-\text{CH}(\text{R}_1)-\text{Y}_1$, in which Y₁ represents an alkali metal atom, a halogeno - magnesium group or a reactive esterified or etherified hydroxyl group, with a reactive derivative of carbonic acid or of formic acid, not more than one of the reactants containing a metal atom; or (b) oxidizing in a compound

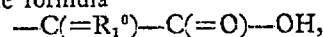
of the formula II in which X₁ represents a grouping of the formula $-\text{CH}(\text{R}_1)-\text{Y}_2$, in which Y₂ represents a hydroxymethyl or borylmethyl group, a formyl group or a 1 - lower alkenyl or lower alkenoyl group, the group represented by Y₂; or (c) reacting a compound of the formula II in which X₁ represents a grouping of the formula $-\text{CH}(\text{R}_1)-\text{Y}_2$, in which Y₂ represents an ammonium group, with a metal cyanide; or (d) decarbonylating a compound of the formula II in which X₁ represents a grouping of the formula $-\text{CH}(\text{R}_1)-\text{Y}_2$, in which Y₂ represents a carboxycarbonyl group; or (e) reacting a compound of the formula II in which X₁ represents an acetyl group, with sulfur in the presence of anionia or a primary or secondary amine; or (f) reacting a compound of the formula II in which X₁ represents a halogeno - carbonyl groups, with an R₁ - diazo compound and rearranging it by hydrolysis, alcoholysis, ammonolysis or aminolysis; or (g) reacting a compound of the formula II in which X₁ represents a 1 - lower alkenyl group, with carbon monoxide and water under acidic conditions; or (h) decarbonylating a compound of the formula II, in which X₁ represents a free or functionally converted grouping of the formula



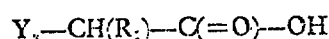
in which R₀ represents a carboxyl group; or (i) converting in a compound of the formula II, in which X₁ represents a free or functionally converted grouping of the formula



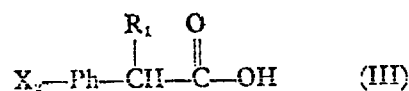
or of the formula



in which R⁰ represents a free or reactive esterified hydroxyl group, and R₁⁰ represents a lower alkylidene or cycloalkylidene group, the group represented by R⁰ into a hydrogen atom or the group represented by R₁⁰ into a group represented by R₁ by reduction; or (k) reacting a compound of the formula II in which X₁ represents a hydrogen atom or a metal atom or a metal grouping, with a reactive ester of a glycolic acid compound of the formula



or a functional acid derivative thereof, in which Y₃ represents a reactive, esterified hydroxyl group; or (m) reacting a compound of the formula





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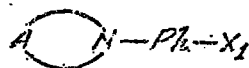
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or a functional acid derivative thereof, as hereinbefore defined in which X_2 represents a reactive, esterified hydroxyl group, with a secondary amine of the formula $A-N-H$ or an

- 5 alkali metal derivative thereof; or (n) reacting a compound of the formula III in which X_2 represents a primary amino group, with a reactive esterified glycol of the formula $HO-A-OH$; and, if desired, converting a
10 resulting ester, amide, thioamide, or nitrile into the corresponding free acid, by hydrolysis; and, if desired, converting, in a resulting compound with a free carboxyl group, the latter into an esterified carboxyl group; and,
15 if desired, converting a resulting compound with a free carboxyl group into an acid halide and reacting the latter with an alcohol, ammonia or an amine; and, if desired, metallizing a resulting ester, salt or nitrile of a
20 compound of the formula I in which R_1 represents a hydrogen atom, in the α -position, and reacting it with a reactive ester of an alcohol of the formula R_1-OH ; and/or if desired, converting a resulting free compound into a
25 salt or a resulting salt into the corresponding free compound; and/or, if desired, resolving a resulting mixture of isomers into the separate isomers.

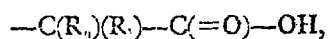
- 30 30. A process for the manufacture of a compound of the formula I as shown in claim 29, in which Ph represents a phenylene radical or a phenylene radical substituted by one or more of the same or different substituents selected from: lower alkyl, free hydroxy, free
35 mercapto, lower alkoxy, lower alkyl-mercapto, halogeno, trifluoromethyl, nitro and amino groups; R_1 represents a 3 to 7 ring-membered cycloalkyl group; and A represents a lower alkylene radical; or a functional acid or amino derivative, as hereinbefore defined,
40 thereof; which comprises (a) reacting a compound of the formula



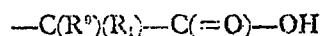
(II)

- 45 in which X_1 represents a grouping of the formula $-CH(R_1)-Y_1$, in which Y_1 represents an alkali metal atom, a halogeno-magnesium group or a reactive, esterified hydroxyl group, with a reactive derivative of carbonic acid or of formic acid, not more than one
50 of the reactants containing a metal atom; or (b) oxidizing in a compound of the formula II, in which X_1 represents a grouping of the formula $-CH(R_1)-Y_1$, in which Y_1 represents a hydroxymethyl or borylmethyl group, a formyl group or a 1-lower alkenyl group, the group represented by Y_2 ; or (d) decarboxylating a compound of the formula II in

which X_1 represents a grouping of the formula $-CH(R_1)-Y_1$, in which Y_1 represents a grouping of the formula $-CH(R_1)-Y_2$, in which Y_2 represents a carboxycarbonyl group; or (e) reacting a compound of the formula II, in which X_1 represents an acetyl group, with sulfur in the presence of ammonia or a primary or secondary amine; or (f) reacting a compound of the formula II in which X_1 represents a halogeno-carboxyl group, with an R_1 -diazo compound and rearranging it by hydrolysis, alcoholysis, ammonolysis or aminolysis; or (n) decarboxylating a compound of the formula II in which X_1 represents a free or functionally converted grouping of the formula



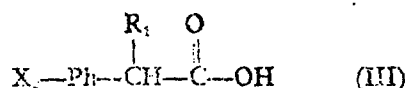
in which R_1 represents a carboxyl group; or (j) converting in a compound of the formula II in which X_1 represents a free or functionally converted grouping of the formula



or of the formula



in which R^a represents a free hydroxyl group, and R_1^a represents a 3 to 7 ring-membered cycloalkylene group, the group represented by R^a into a hydrogen atom or the group represented by R_1^a into a group represented by R_1 , by reduction; or (m) reacting a compound of the formula



or a functional acid derivative thereof, in which X_2 represents a reactive esterified hydroxyl group, with a secondary amine of

the formula $A-N-H$ or an alkali metal

derivative thereof; or (n) reacting a compound of the formula III in which X_2 represents a primary amino group, with a reactive esterified glycol of the formula $HO-A-OH$; and, if desired, converting a resulting ester, amide, thioamide or nitrile into the corresponding free acid by hydrolysis; and, if desired, converting in a resulting compound with a free carboxyl group, the latter into an esterified carboxyl group; and, if desired, converting a resulting compound with a free carboxyl group into an acid halide and reacting the latter with an alcohol, ammonia or an amine; and, if desired, metallizing a resulting ester, salt or nitrile of a compound of the formula I in which R_1 represents a hydrogen atom, in the α -position, and reacting it with a reactive

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ester of an alcohol of the formula R_1-OH ; and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the corresponding free compound; and/or, if desired, resolving a resulting mixture of isomers into the separate isomers.

31. A process as claimed in claim 30, wherein, in method (a), Y_1 represents an alkali metal atom or a halogenomagnesium group, and the compound of formula II is reacted with carbon dioxide, a carbonate, a halogenoformic acid ester, a cyanogen halide or a carbamoyl halide.

32. A process as claimed in claim 29, wherein, in method (a), Y_1 represents an alkali metal atom or a halogeno-magnesium group, and the compound of formula II is reacted with carbon dioxide, a carbonate, a halogenoformic acid ester, a cyanogen halide, a carbamoyl halide, carbon disulphide or diethyl thiocarbonate.

33. A process as claimed in claim 30, wherein, in method (a), Y_1 represents a reactive esterified hydroxyl group, and the compound of formula II is reacted with a metal cyanide.

34. A process as claimed in claim 29, wherein, in method (a), Y_1 represents a reactive esterified hydroxyl group, and the compound of formula II is reacted with a metal cyanide.

35. A process as claimed in claim 30, wherein, in method (b), Y_2 represents a hydroxymethyl or borylmethyl group, a formyl group or a 1-lower alkenyl group and the compound of formula II is oxidized with hydrogen peroxide or a heavy metal salt or oxide.

36. A process as claimed in claim 29, wherein, in method (b), Y_2 represents a hydroxymethyl or borylmethyl group, a formyl group or a 1-lower alkenyl or a lower alkenoyl group, and the compound of formula II is oxidized with hydrogen peroxide or a heavy metal salt or oxide.

37. A process as claimed in claim 29, wherein, in method (d), Y_2 represents a carboxycarbonyl group, and the compound of formula II is pyrolyzed.

38. A process as claimed in claim 30, wherein P_1 represents a carboxy group and the starting material is pyrolyzed under acidic conditions.

39. A process as claimed in claim 29, wherein, in method (n), R_1 represents a carboxy group, and the compound of formula II is pyrolyzed under acidic conditions.

40. A process as claimed in claim 30, wherein, in method (i), R^0 represents a hydroxyl group and R_1^0 represents a 3 to 7 ring membered cycloalkylidene group and the compound of formula II is treated with catalytic-

ally activated or nascent hydrogen, or a compound of formula II in which R^0 represents a hydroxy group is treated with phosphorus and iodine, hydriodic acid or stannous chloride.

41. A process as claimed in claim 29, wherein, in method (i), R^0 represents a free or reactive esterified hydroxy group and R_1^0 represents a lower alkylidene or cycloalkylidene group and the compound of formula II is treated with catalytically activated or nascent hydrogen, or a compound of formula II in which R^0 represents a hydroxy group is treated with phosphorus and iodine, hydriodic acid or stannous chloride.

42. A process as claimed in claim 29, wherein, in method (k), X_1 represents a hydrogen atom and the reaction is carried out in the presence of aluminium chloride.

43. A process as claimed in claim 30, wherein, in method (m), X_2 stands for a fluorine atom.

44. A process as claimed in claim 29, wherein, in method (m), X_2 stands for a fluorine atom.

45. A process as claimed in claim 30, wherein, in method (n), a lower alkylene dihalide is used as the reactive esterified glycol of the formula $HO-A-OH$.

46. A process as claimed in claim 29, wherein, in method (n), a lower alkylene dihalide is used as the reactive esterified glycol of the formula $HO-A-OH$.

47. A process as claimed in claim 29, wherein, in method (n), a reactive, functional acid derivative corresponding to the glycol of claim 29 is used.

48. A compound as claimed in claim 4 or 5, whenever prepared by the process claimed in any one of claims 30, 31, 33, 35, 38, 40, 43 and 45.

49. A compound as claimed in claim 1 or 2, whenever prepared by the process claimed in any one of claims 29, 32, 34, 36, 37, 39, 41, 42, 44, 46 and 47.

50. α -(3-chloro-4-piperidino-phenyl)- α -cyclopropyl-acetic acid.

51. A salt of the compound claimed in claim 50.

52. A physiologically tolerable salt of the compound claimed in claim 50.

53. A pharmaceutical preparation comprising any one of the compounds claimed in claim 50 or 52 in admixture or conjunction with a pharmaceutically acceptable carrier.

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