ABSTRACT OF THE DISCLOSURE

The compounds are of the class of 4-(1-pyrpyl)-phenyl-alkanoic acid and the pharmaceutically acceptable salts thereof and have analgesic and anti-inflammatory activity; the compounds are active ingredients of pharmaceutical compositions and are useful for alleviating pain and treating inflammatory diseases in mammals; an illustrative embodiment is 4-(1-pyrpyl)-3-chlorophenyl]-butyric acid.

DETAILED DESCRIPTION

The present invention invention concerns substituted phenylalkanoic acids and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing these compounds and methods of alleviating pain and treating inflammatory diseases in mammals comprising administering them.

More particularly, the present invention concerns 4-(1-pyrpyl)-phenyl]-alkanoic acids of the formula

wherein:
Z is the —CH₂ — or the —CO— group, and
R₁ is hydrogen or halogen up to the atomic number 35, and pharmaceutically acceptable salts thereof with inorganic and organic bases.

In the compounds of Formula I and the starting materials mentioned below, R₂ as halogen up to the atomic number 35 can be fluoro, chloro or bromo, and is preferably chloro.

A preferred subclass are compounds of Formula I, wherein Z is the —CH₂ — group and R₁ is hydrogen or chloro, as well as the pharmaceutically acceptable salts thereof.

Preferred members of the compounds of Formula I are 4-(1-pyrpyl)-3-chlorophenyl]-butyric acid, 4-(1-pyrpyl)-phenyl]-butyric acid, 3-(1-pyrpyl]-benzoyl]-propionic acid and the pharmaceutically acceptable salts thereof.

The compounds of the present invention were found to have valuable pharmaceutical properties, in particular, analgesic, anti-inflammatory and antipyretic activity, combined with a favorable therapeutic index. The pharmacological activity of the compounds of the invention is determined in various standard tests with experimental animals.

The analgesic activity is demonstrated in the “writhing test” in mice. This test is described by E. Siegmund, R. Cadmus and G. Lu, Proc. Soc. Exp. Biol. Med. 95, 729 (1957). The amount of test substance is determined preventing in the test animals the syndrome produced by intraperitoneal injection of 2-phenyl-1,4-benzoxiquone.

Excellent results are obtained by oral administration of 55 mg./kg. of bodyweight of 4-(1-pyrpyl)-3-chlorophenyl]-butyric acid.

As an example of the use as anti-inflammatory agent, the use of 4-(1-pyrpyl]-3-chlorophenyl]-butyric acid in bolus alba induced edema in the rat paw is described. The test used is that described by G. Wilhelm, Jap. Journ. Pharmac. 15, 190 (1965). The compound under investigation is administered to rats perorally through an esophageal sound. One hour thereafter, bolus alba edema is induced by subcutaneous injection of 0.1 ml. of a 10% suspension of finely sieved bolus alba in tragacanth into the plantar region of the right hand paw of the rats. Another group of rats having not obtained the test compound, but the bolus alba, serves as control group. Each group consists of 20 male albino rats weighing about 110 to about 130 g. The intensity of the swelling of the rats' paw is determined 5 hours after the bolus alba injection, by measuring the weight differences of the unwollen left paws and the swollen right paws. Thus it is determined that 4-(1-pyrpyl]-3-chlorophenyl]-butyric acid administered in a dosage of about 25 mg./kg. of bodyweight significantly inhibits the formation of the bolus alba edema indicating a pronounced anti-inflammatory activity.

Similar analgesic and anti-inflammatory activities are found with other compounds of the invention.

The toxicity of the compounds of the invention on oral administration is of favorable low order.

The new, substituted alkanoic acids of the general Formula I and their pharmaceutically acceptable salts with inorganic and organic bases are suitable as active substances for medicaments, which can be administered orally, rectally or parenterally, for the relief and removal of pains of varying origin and for the treatment of rheumatic and other inflammatory diseases.

The new, substituted alkanoic acids of the general Formula I and their salts are produced by reacting a compound of the general Formula II

wherein R₁ and Z have the meaning given under Formula I, or a salt thereof with monomeric or polymeric succinylaldehyde or with an open or cyclic, reactive functional derivative of the monomeric succinylaldehyde and, optionally, converting an obtained acid of the general Formula I into a salt with an inorganic or organic base. The succinic aldehyde is added in its monomeric form (which immediately before the reaction is obtained from a functional derivative or from distillation of polymeric form), or in a polymeric modification (cf. C. Harries Ber. 35, 1183-1189 (1902)). As functional derivatives of the monomeric succinic aldehyde are used preferably open or cyclic acetals, acylals, x-halogen ethers, esters or enol esters corresponding to the general Formula III

in which:
X and X' are independently of each other, rests of formulae R—O—and R—CO— in which R stands for an optional halogen substituted hydrocarbon rest, or chlo-
rime or bromine atoms, or X' together with Y' is also the oxo rest = 0.

Y and Y' are independently of each other, rests of the before defined formulae R—O— or R—CO—O— or both of these oxo rest = 0, or each together with Z and Z' respectively each an additional binding according to the dotted lines and

Z and Z' are hydrogen atoms if they do not have one of the before mentioned meanings,
in the presence or absence of a diluent and/or condensation agent.

Of the compounds of the general Formula III which can be in place of succinic aldehyde, are mentioned as examples of open-chain derivatives of the monomeric succinic aldehyde the acetals of the latter such as succinic aldehyde - mono - diethylacetal, -bis-dimethylacetal, -bis-diethylacetal, also acylals thereof such as succinic aldehyde-1,1-diacetate (4,4'-diacetoxybutylaldehyde), enol ethers thereof such as 1,4-diphenoxbutadiene, and enol esters thereof such as 1,4-diacetoxybutadiene. Compounds of the general Formula III, wherein Y and Y' together form the epoxy radical, are strictly derivatives of tetrahydrofurans which, depending on the meaning of X and X', react like the acetals or acylals of the succinaldehyde or like open-chain α-halogen ethers. Such compounds are, e.g., the 2,5-dialkyoxetetrahydrofurans and related compounds such as 2,5-dimethoxy, 2,5-diethoxy, 2,5-diproxy, 2,5-dibutoxy, 2,5-bisallyloxy, 2,5-bis-(2-chloroethoxy), 2,5-diphenoxy and 2,5-bis-(3,4-xylolyloxy)-tetrahydrofurans, also 2,5-diacetoxytetrahydrofurans such as 2,5-diacetoxytetrahydrofurans, as well as 2,5-dihalo- genetetrahydrofurans such as 2,5-dichloroetetrahydrofurans and 2,5-dibromotetrahydrofurans and, finally, also compounds which simultaneously belong to two types, such as 2-chloro-5-(2-chloroethoxy)-tetrahydrofurans and 2-allyloxy-5-chlorotetrahydrofurans.

As a medium for the reaction according to the invention, when using free succinaldehyde or succinaldehydes liberated in situ, any solvent is suitable in which the latter is soluble, e.g., water, methanol, ethanol or acetic acid. Acetals and acylals of the succinaldehyde, as well as cyclic, acetal-like derivatives, are advantageously reacted in acetic acid as the solvent and condensation agent, e.g., in the presence of catalytic amounts of an acid condensation agent such as p-toluene sulfonic acid, in the presence or absence of an inert organic solvent or diluent such as, e.g., xylol, toluene, o-dichlorobenzene or acetanilide. The reaction of compounds of the general Formula III wherein X and X' are halogen atoms, is performed, e.g., in inert organic solvents such as chloroform or those mentioned above. The reaction temperature is preferably between room temperature and boiling temperature of the applied solvent or diluent, whereby the lowest range is suitable, especially in the case of the latter mentioned halogen compounds.

Of the starting substances of the general Formula II, the 4-(p-aminophenyl)-butyric acid and the 3-(p-aminobenzoyl)propiolic acid are known. It is possible to produce 4-(4-amino-3-halogenphenyl)-butyric acids, such as the 4-(4-amino-3-chlorophenyl)-butyric acid, from the likewise known 4-(p-aminomethyl)-butyric acid by halogenation, e.g., chlorination by means of hydrochloric acid and an alkali chloride, and subsequent hydrolysis.

According to a second process, the new, substituted alkanolic acids of the general Formula I and their salts are produced by heating a substituted malonic acid of the general Formula IV amount of carbon dioxide has been liberated and, optionally, converting an obtained free monocarboxylic acid of the general Formula I into a salt with an inorganic or organic base. Decarboxylation according to the process is performed by heating a substituted malonic acid of the general Formula IV or, e.g., an acid alkali salt as such, optionally under vacuum, to temperatures between ca. 160° and 220° until the evolution of carbon dioxide has ceased. The decarboxylation can, however, also be carried out by heating in a higher-boiling organic solvent such as, e.g., o-dichlorobenzene, tetralin or diethyl glycol dimethylether, and/or accelerated by the addition of catalysts such as, e.g., copper powder, or of organic bases such as, e.g., quinoline.

The substituted malonic acids of the general Formula IV, which are required as direct starting materials are obtained by hydrolysis of correspondingly substituted malonic acid dialkyl esters or cyanoacetic acid dialkyl esters, e.g., by boiling of the latter in alkanolic or alkanolic-aqueous alkali hydroxide solutions such as, e.g., methanolic potassium hydroxide solution, and subsequent liberating of the dicarboxylic acid. The correspondingly substituted malonic acid dialkyl esters and cyanoacetic acid alkyl esters are produced, for example, by the condensation of reactive esters of p-(1-pyrrol)-phenethyl alcohol or -2 - hydroxycetophenone, optionally substituted according to the definitions for R₁, e.g., by condensation of corresponding p-(1-pyrrol)-phenethyl halides, p-toluene sulfonic acid p-(1-pyrrol)-phenethyl esters or p-(1-pyrrol)- phenacyl halides, with sodium compounds of lower malonic acid dialkyl esters, especially malonic acid diethyl ester, or lower cyanoacetic acid alkyl esters in suitable organic solvents such as, e.g., dimethylformamide, dimethyl sulfoxide, ethanol, butanol or benzene. The reactive esters of p-(1-pyrrol)phenethyl alcohol, optionally substituted as defined and which are required for this reaction, are produced from the corresponding alcohols in the usual manner, e.g., by treatment with thionyl chloride, phosphorus trichloride or p-toluene sulphonyl chloride in pyridine. The unsubstituted p-(1-pyrrol)-phenethyl alcohol, and those substituted according to the definition for R₁, are obtained from the correspondingly aromatic acetophenyl esters by acetylation with functional derivatives of the succinic aldehyde analogously to the first mentioned process for producing compounds of the general Formula I. If the ring closure is performed in a lower alkanoic acid such as, e.g., acetic acid, then as reaction product is obtained, in addition to the desired p-(1-pyrrol)-phenethyl alcohol, the corresponding lower alkanoic acid ester thereof, so that the crude product must be firstly subjected to hydrolysis, e.g., by boiling in an alkanolic alkali solution. The subsequent operation referred to can be avoided by using other reaction media, e.g., acetonitrile with a small addition of p-toluene sulfonic acid. By ring closure, analogously to the first stated process for the production of the compounds of the general Formula I, the corresponding p-(1-pyrrol)-phenacyl halides are obtained starting with p-aminophenacyl halides.

Of the p-aminophenyl compounds required for the ring closure, the p-aminophenylalcohol and the 2-chloro-4'-amino-acetophenone (p-aminophenacyl chloride) are known. The compounds with a halogen atom in the 3 position are obtained e.g. by acetylation in the amino group of the (p-aminophenyl)-acetic acid, the obtained N-acetyl derivatives halogenated, e.g., chlorinated by treatment with hydrochloric acid and sodium chloride, and the corresponding lower 2 (4-amino-3-halogen phenyl)-alkanoic acids obtained are reduced to the corresponding alcohols by means of lithium aluminium chloride.

According to a third process, the new substituted phenylalkanoic acids and their salts, which are embraced by the general Formula I, wherein Z means the —CH₂—
The compounds of the general Formula Ia are reduced, for example, according to the Wolff-Kishner method, with hydrazine or semicarbazide in the presence of an alkali hydroxide or alkali metal alcoholate at elevated temperature and, optionally, the freshly obtained alkali salt of the 4-[1-(1-pyrryl)-phenyl]-butyric acid, optionally halogen-substituted and embraced by the general Formula I, is converted into the free acid or into another salt with an inorganic or organic base.

The reduction is performed by bringing the stated reaction components together, preferably in a higher-boiling organic solvent, and heating the mixture to temperatures between 140° and 200°. Suitable as a reaction medium are, e.g. mono and diethers of ethylene glycol such as diethylene glycol, its monomethyl ether and triethylene glycol, also higher-boiling alcohols such as benzyl alcohol, octyl alcohol and nitritoltriethanol or, optionally, also a lower alkanol, providing that the reduction is carried out in a closed vessel.

A further suitable reduction method is the process according to Clemmensen. For example, a compound of the general Formula Ia is refluxed for several hours with a large excess of amalgamated zinc having an enlarged surface area, e.g. zinc wool, in excess hydrochloric acid, initially ca. 4 N to 8 N, preferably in the presence of a solvent not miscible with water such as, e.g. toluene, and/or a water-miscible solvent such as, e.g. acetic acid, whereby from time to time some concentrated hydrochloric acid is added.

The compounds of the general Formula Ia, required as starting materials, are, for their part, already embraced by the general Formula I and they are obtainable using the aforesaid processes for the production of these compounds. For example, they can be obtained starting with acetaldehyde or α-haloacetaldehydes by reaction with succinic anhydride according to the Friedel-Crafts reaction, to give the 3-(p-acetamidobenzoyl)-propionic acid or 3 - (4-acetamido - 3 - halogen benzoyl) - propionic acids, by hydrolytic splitting off of the N-acetyl group and by condensation of the obtained 3-(p-acetamidobenzoyl)-propionic acid or 3 - (4-amino - 3 - halogen benzoyl)-propionic acids with functional derivatives of the succinimide, e.g. with 2,5-dimethoxytetrahydrofuran, corresponding to the first mentioned process for the production of the compounds of the general Formula I. In the other hands, the aforesaid 3-(4-acetamidobenzoyl)-propionic acid or its halogen derivatives are reduced analogously to the compounds of the general Formula Ia, according to Wolff-Kishner or Clemmensen, then from this is obtained, with simultaneous splitting off of the N-acetyl group, the 4 - (p - aminophenyl) - butyric acid or 4 - (4-amino - 3 - halogen phenyl) - butyric acids, i.e. compounds of the general Formula II which can be used as starting materials for the first mentioned process for the production of the end materials.

Optionally producable pharmaceutically acceptable salts of substituted alkanic acids of Formula I are e.g. the sodium, potassium, lithium, magnesium, calcium and ammonium salts, as well as salts with ethylamine, triethylamine, 2-aminoethanol, 2,2'-iminodiethanol, 2-dimethylaminopropanol, 2-diethylaminopropanol, ethylidine diamine, benzylamine, propionic, pyrolidine, piperidine, morpholine, 1-ethyl piperidine or 2-piperidinoethanol, or with basic ion exchangers. The salts are produced via conventional methods.

Pharmaceutical preparations according to the present invention contain, as active ingredient, at least one compound of Formula I or a pharmaceutically acceptable salt thereof in combination with an inert carrier and, if desired, other additives. The inventive compositions consist, preferably, of dosage unit forms which are suitable for the oral, rectal or parenteral application of daily doses of 1–80 mg./kg. of a compound of Formula I for mammals. Suitable dosage unit forms for the oral or rectal application, such as drages, tablets, capsules, suppositories or
ampoules respectively, contain preferably 10 to 500 mg. of a compound of Formula I or of a pharmacologically acceptable salt thereof.

In dosage units for oral administration, the content of active substance is preferably between 10% and 90%. Such dosage units are produced by combining the active substance with, e.g., solid pulverent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants, such as magnesium stearate or polyethylene glycols, to form tablets or dragee cores. The drugs are coated, for example, with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosages of active substance. Other suitable dosage units for oral administration are hard capsules made of gelatine, as well as soft closed capsules made of gelatine and a softener such as glycerin. The hard capsules preferably contain the active substance as a granulate in admixture with lubricants such as talcum or magnesium stearate and, optionally, stabilisers such as sodium metabisulphite (Na₂S₂O₅) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, whereby stabilisers can also be added.

Suitable dosage units for rectal administration are, e.g. suppositories which consist of a combination of an active substance with a suppository foundation substance based on natural or synthetic triglycerides (e.g. cocoa butter), polyethylene glycols or suitable higher fatty alcohols, and gelatine rectal capsules containing a combination of the active substance and polyethylene glycol 3000. Ampoules solutions for parenteral, particularly intramuscular or intravenous administration contain, e.g. an aqueous solution of 0.5–5% of a pharmaceutically acceptable, water-soluble salt of an acid of the general formula I.

Also embraced by the present invention are pharmaceutical compositions not made up in single dosage unit forms such as ointments,ointments and other mixtures for local or parenteral application, which can be prepared with known foundations for ointments or pharmaceutically acceptable solvents by methods of alleviating pain and treating inflammatory diseases in mammals which methods comprise administering an effective amount of at least one compound of the invention, preferably in form of an inventive pharmaceutical composition.

It is to be understood that the dosage administered will be dependent on the species, the age, health and weight of the recipient; the severity of the condition being treated; the kind of concurrent treatment, if any; the frequency of treatment and the nature of the effect desired. Generally, the daily dosage of an active compound of Formula I, as a weight of about 80 mg./kg. bodyweight. A preferred range is about 80 mg./kg. bodyweight per day.

The following examples will serve to further typify the nature of the present invention, but should not be construed as a limitation on the scope thereof.

EXAMPLE 1

A mixture of 16.5 g. of crude 4-(4-amino-3-chlorophenyl)-butyric acid (see below) and 10.2 g. of 2,5-dimethoxytetrahydrofuran is dissolved in 22 ml. of glacial acetic acid and is refluxed for 40 minutes. The reaction mixture is then cooled to room temperature and dissolved in 300 ml. of ether. The ethereal solution is decanted to remove negligibly adhesive by-products and is then washed, firstly with 55 ml. of a 3 N hydrochloric acid, and twice with 1 N hydrochloric acid using each time 25 ml. The ethereal solution is then extracted with 220 ml. of 1 N sodium hydroxide solution. The ether phase is discarded and the aqueous phase is washed twice with 200 ml. of ether. The aqueous phase is then acidified with 80 ml. of 3 N hydrochloric acid and subsequently extracted, firstly with 200 ml. of ether. The ether solution is then concentrated by evaporation to dryness and the residue is distilled in high vacuum, whereby the 4-(4-(1-pyrrol)-3-chlorophenyl)- butyric acid, B.P. 177°/0.07 torr, M.P. 58–60°, nD₂₀=1.5803, is obtained. Positive Ehrlich-reaction.

The 4-(4-amino-3-chlorophenyl)-butyric acid, required as starting material, is produced as follows:

(a) An amount of 40.0 g. of 4-(p-acetamidophenyl)-butyric acid (M. N. Bogdanov et al., Vysokomolek. Soedin. 3, 1326 (1961)) is suspended in a mixture of 70 ml. of acetic acid and 75 ml. of concentrated hydrochloric acid. Whilst stirring vigorously, a solution of 7.0 g. of sodium chloride in 8.5 ml. of water is added dropwise at –10° within 45 minutes. The obtained suspension is heated to 0° and stirred for 15 minutes at this temperature. An addition is then made of 50 ml. of hydrochloric acid and the mixture is refluxed for 2 hours. The reaction solution is concentrated by evaporation to dryness on the water bath (100°) under 10 torr. The residue is dissolved, as far as possible, in water, is filtered off from undissolved matter and the filtrate washed twice with, each time, 20 ml. of water. The filtrate and washing water are combined and the pH value adjusted to 4 by the addition of 3 N sodium hydroxide solution. The obtained dispersion is extracted with ether, the ether solution is dried and concentrated by evaporation, whereby 30.5 g. of oily crude product are obtained. The latter is dissolved in 100 ml. of 3 N sodium hydroxide solution and the solution washed twice with, together, 100 ml. of ether. After acidifying with 65 ml. of concentrated hydrochloric acid, the aqueous phase is extracted four times with, each time, 100 ml. of ether and, by the addition of 3 N sodium hydroxide solution (130 ml.), the pH value is adjusted to 3. The precipitated oil is dissolved in ether by extraction with three portions each of 150 ml. The combined ether solutions are dried over magnesium sulphate and concentrated by evaporation to dryness. This yields 19.3 g. (50% of theoretical amount) of crude 4-(4-amino-3-chlorophenyl)-butyric acid, M.P. 65–69°, which can be directly further reacted. After crystallising several times, firstly from water/ethanol and then from benzene/cyclohexane, the analytically pure substance, M.P. 70–74°, is obtained.

EXAMPLE 2

A mixture of 11 g. of crude, oily [3-chloro-4-(1-pyrrol)-phenethyl]-malonic acid diethyl ester are refluxed for 6 hours with a solution of 12 g. of potassium hydroxide in 10 ml. of ethanol and 70 ml. of water. The solvent is then distilled off under reduced pressure. The concentrated residue is distributed between 100 ml. of ether and 200 ml. of water. The aqueous phase is separated, filtered and adjusted to pH 1–2 with concentrated hydrochloric acid. The pre-
cipated acid is extracted twice using, each time, 100 ml of ether. The ether extract is dried and concentrated by evaporation. The thus obtained crude, oily 3-chloro-4-(1-pyrryl)-phenethyl-malonie acid is heated gradually to 160–200° (ca. 20 minutes). When the evolution of gas has ceased, the product is distilled in a bulb tube at 160–170°/0.01 torr. The pure 4-[3-chloro-4-(1-pyrryl)-phenethyl-butryic acid melts at 58–60° (from isopropanol).

The substituted malonic ester, required as starting material, is produced by way of the following stages:

(a) 149.0 g. p-acetamido-phenylethanoic acid (S. Gabriel, Chem. Ber. 15, 834 (1882)) are suspended in a mixture of 485 ml. glacial acetic acid, 165 ml. water and 348 ml. conc. hydrochloric acid. To this mixture is dropped, while strongly stirring at −5°, a solution of 32.3 g. sodium chloride in 65 ml. water within 1 hour. The reaction mixtures brought to 0° and stirred for 15 minutes. Then there are added 75 ml. conc. hydrochloric acid, the solution is refluxed for 2 hours and then evaporated, on a steam bath of 80° and under 15 torr, to dryness. The residue from evaporation is mixed hot with 250 ml. ethanol to remove the last water by acetone distillation and to this mixture are added 750 ml. benzene and then it is evaporated in vacuo again. The dry crystalline residue is refluxed with a solution of 60 ml. conc. hydrochloric acid in 1.5 l. abs. ethanol for 20 hours. The ethanol is then distilled off in a bath of 30° and 15–20 torr. The residue which is obtained after evaporation is brought to pH 9–10 with a mixture of same amount of ice and concentrated sodium hydroxide and extracted with 1.5 l. methylcellophane. The methylenechloride solution is washed with 100 ml. ice water dried over magnesium sulfate and evaporated. The residue of the evaporation is subjected to fractional distillation using a 10 cm. long Vigreux column and the (4-amino-3-chloro-phenyl)-acetic acid ethyl ester (83 g.) which boils at 110–115°/0.001 torr is separated.

(b) 55.5 g. (4-amino-3-chloro-phenyl)-acetic acid ethyl ester, 500 ml. glacial acetic acid and 34.3 g. 2.5-dimethoxy-tetrahydrofuran are refluxed for 40 minutes. The cooled reaction mixture is evaporated under reduced pressure, finally under 10 torr at a bath temperature of 70°. The resulting black oil is distilled in a bulb tube that boils under 0.01 torr at an air bath temperature of 120–130°. The obtained 3-(chloro-4-(1-pyrryl)-phenyl)-acetic acid ethyl ester crystallises on longer standing or if inoculated. A sample recrystallised from ligroin (boiling range 80–95°) melts at 36–37°.

(c) A mixture of 62.0 g. 3-chloro-4-(1-pyrryl)-phenyl)-acetic acid ester, 200 ml. toluene and 260 ml. diethylcarbamate is warmed to 70°. At 75–80° a solution of 5.6 g. sodium in 200 ml. abs. ethanol is dropped rapidly through while stirring. The ethanol is thereafter distilled off from the reaction mixture.

(d) 2.2 g. lithium aluminium hydride are suspended in 200 ml. abs. ether. While stirring, a solution of 15.0 g. 3-chloro-4-(1-pyrryl)-phenyl-acetic acid ethyl ester [see Examples 3(a) and (b)] in 300 ml. abs. ether, is dropped into the reaction mixture in such a way that the reaction mixture refluxes. After the addition of the ester the reaction mixture is refluxed while stirring for 10 hours. Then it is decomposed while cooling with ice by addition of 15 ml. water and then of 50 ml. 20% hydrochloric acid. The ether phase is separated, washed with 50 ml. 10% potassium bicarbonate solution, dried over magnesium sulfate and evaporated. The oil resulting reaction product, can be recrystallised from ether and is distilled from benzene (B. 45–60°). The obtained 3-chloro-4-(1-pyrryl)-phenyl-ethyl alcohol melts at 59–61°.

(e) 2.0 g. of p-toluene sulphonic acid-[3-chloro-4-(1-pyrryl)-phenethyl ester] and 4.5 g. of sodium propionate are reacted analogously to Example 24. By bulb-bulb distillation the crude product at 110°/0.001 torr, the propanol 3-chloro-4-(1-pyrryl)-phenethyl-propionate ester is obtained.

The p-toluene sulphonic acid-[3-chloro-4-(1-pyrryl)-phenethyl phenyl ester] is produced according to E. Jenny and S. Weinstein, Helv. Chim. Acta 41, 820 (1958) from 1.8 g. of 3-chloro-4-(1-pyrryl)-phenethyl alcohol (cp. Example 4) and 2.0 g. of p-toluene sulphonylic acid chloride in 10 ml. of pyridine. The compound is oily. It is chromatographed on silica gel (activity grade F-254, E. Merck) 8.0 g. of malonic acid diethyl ester, dissolved in 100 ml. of dimethyl sulphoxide, are mixed in the course of 15 minutes with 2.1 g. of a 50% sodium hydride dispersion in mineral oil and the mixture is stirred for 4 hours. A solution of 18.8 g. of p-toluene sulphonylic acid-[3-chloro-4-(1-pyrryl)-phenethyl phenyl ester] in 60 ml. of the dimethyl sulphoxide is then added. The reaction mixture is stirred for 5–7 hours at 100° bath temperature. After neutralising with glacial acetic acid, the solvent is distilled off under 10 torr in a bath at 80–100°. The concentrated residue is distributed between 300 ml. of ether and 100 ml. of water. The ether layer is separated, dried and concentrated by evaporation. This yields the crude 3-chloro-4-(1-pyrryl)-phenythyl-malonie acid diethyl ester as a brown oil, which is further processed in the crude form.

**EXAMPLE 4**

3.4 g. of 4-[p-(1-pyrryl)-phenyl]-butyronitrile, 3.3 g. of sodium hydride, 30 ml. of ethanol and 10 ml. of water are refluxed together for 18 hours. The solvent is then distilled off under reduced pressure in a rotary evaporator. The residue is taken up in 30 ml. of water and extracted with 70 ml. of ether. The aqueous phase is separated and acidified with 7 ml. of concentrated hydrochloric acid whilst cooling with ice. The precipitated colourless crystals are filtered with suction and washed with 5 ml. of ice water. After drying under 20 torr over sulphuric acid, 3.0 g. of crude 4-[p-(1-pyrryl)-phenyl]-butyric acid, M.P. 109–114°, are obtained. The pure acid, M.P. 113–114°, is obtained by crystallisation from isopropanol.

The butyronitrile, required as starting material, is obtained by way of the following stages:

(a) 76.0 g. of p-nitrocinamic acid ethyl ester are hydrogenated in 750 ml. of ethanol in the presence of 10 g. of Raney nickel at room temperature and under normal pressure. After 24 hours, the calculated amount of hydrogen has been absorbed. The catalyst is filtered off and the filtrate is concentrated by evaporation. The residue is distilled in high vacuum, The (3-p-aminophenyl)-propionic acid ethyl ester boils at 121–123°/0.02 torr.

(b) 9.7 g. of 3-(p-aminophenyl)-propionic acid ethyl ester, 6.6 g. of 2.5-dimethoxy-2,4-pentanediol and 50 ml. of glacial acetic acid are refluxed for 45 minutes. The residue remaining after distilling off the glacial acetic acid in the water-jet vacuum, is distilled in a bulb tube at ca. 130° bath temperature and 0.05 torr. This yields 9.2 g. of 3-[p-(1-pyrryl)-phenyl]-propionic acid ethyl ester as a yellowish oil, which gradually solidifies to form a crystalline substance.

(c) From 23.0 g. of 3-[p-(1-pyrryl)-phenyl]-propionic acid ethyl ester and 3.8 g. of lithium aluminium hydride in 700 ml. of absolute ether are produced, analogously to Example 4, 18.0 g. of 3-[p-(1-pyrryl)-phenyl]-1-propanol, M.P. 84–86°.

(d) 17.8 g. of 3-[p-(1-pyrryl)-phenyl]-1-propanol are dissolved in 90 ml. of anhydrous pyridine and to this solution are added in portions, while stirring and at 5–10°, 19.0 g. of p-toluene sulphonylic acid chloride. The reaction mixture is then stirred overnight at room temperature. The pyridine is evaporated off under reduced pressure. The residue is distilled in 250 ml. of methylene chloride and the solution washed successively, twice with 2 N sodium hydroxide solution using 50 ml. each time, twice with 2 N hydrochloric acid using 50 ml. each time and, finally, with 50 ml. of water. After drying over magnesium sulphate, the methyllithium chloride is distilled off, when 13.7 g. of a partially crystalline substance remain. This is applied to a column of 280 g. of silica gel and is extracted with
benzene (50 ml. fractions). The fractions 2–14 contain 6.9 g. of 1-chloro-3-[(1-pyrryl)-phenyl]-propene, M.P. 67–69°. This is used for the following test. The fractions 19–32 contain 3.2 g. of p-toluene sulphonate acid-3-[(1-pyrryl)-phenyl]-propyl ester, M.P. 78–79° (from ethanol) (c). 5.1 g. of 1-chloro-3-[(1-pyrryl)-phenyl]-propene are dissolved in 60 ml. of dimethyl sulphoxide and are stirred under nitrogen with 1.3 g. of sodium cyanide for 4 hours at 100–110°. The reaction mixture is now cooled, stirred together with 60 ml. of water and extracted twice with ether using 300 ml. each time. The ether extracts are combined, washed with 30 ml. of water, dried (MgSO₄) and concentrated by evaporation. The crystalline residue is crystallised from 10 ml. of isopropanol and yields 3.5 g. of 4-[(1-pyrryl)-phenyl]-butyronitrile, M.P. 96–99°.

**EXAMPLE 5**

18.9 g. of 3-(p-aminobenzoyl)-propionic acid [cp. J. Am. Chem. Soc. 67, 2264 (1945)], 12.9 g. of dimethoxytetrahydrofuran and 41 ml. of glacial acetic acid are mixed together and refluxed for 15 minutes. The hot reaction mixture is cooled and allowed to stand for about 15 hours. The precipitate, slightly yellowish-brown crystals are filtered off, washed twice with acetic acid using 15 ml. each time, then with 15 ml. of methanol and 30 ml. of ether, and dried at 70°. The obtained 3-[(1-pyrryl)-benzoyl]-propionic acid melts in an evacuated tube at 191–195°. Recrystallisation from isopropanol and decolourisation with activated charcoal yield white crystals, M.P. 193–194°. The substance produces a positive Ehrlich-reaction and an orange-red precipitation with dinitrophenyl hydrazine in hydrochloric acid.

**EXAMPLE 6**

(a) 3.6 g. of 4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester and 20 ml. of 2 N sodium hydroxide solution are refluxed for ½ hour and stirred. After cooling, the homogeneous reaction solution is extracted with 20 ml. of ether. The aqueous phase is made acidic with 4–5 ml. of concentrated hydrochloric acid. The 4-[(1-pyrryl)-phenyl]-butyric acid hereby precipitates. It is filtered off, washed with water and recrystallised from isopropanol, M.P. 113–114°.

The 4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester, required as starting material, is produced in the following manner:

(b) 1.0 g. of hydrochloric acid gas is introduced at 0 to 5° into a solution of 4.2 g. of 4-[(1-pyrryl)-phenyl]-butyronitrile (cp. Example 4) in 1.5 ml. of absolute alcohol and 10 ml. of methylene chloride. The reaction mixture is left closed for 2 days at 0 to 5° and then 10 ml. of ether are added to the mixture. The 4-[(1-pyrryl)-phenyl]-butyric acid-imido-ethyl ester hydrochloride precipitates out. An addition of 30 ml. of 2 N sodium hydroxide solution and 100 ml. of ether is now made and the whole is vigorously shaken for 3 minutes. The organic phase is then separated, washed with 20 ml. of water, dried over magnesium sulphate and concentrated by evaporation. Then the 4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester, which is purified by distillation in the bulb tube at 140°/0.001 torr; nD²⁰=1.553.

The 4-[(3-chloro-4-[(1-pyrryl)-phenyl]-butyric acid, M.P. 58–60° (from isopropanol), is produced, analogously to Example 6, by hydrolysis of 1.0 g. of 4-[(3-chloro-4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester with 5 ml. of 2 N sodium hydroxide solution.

The 4-[(3-chloro-4-[(1-pyrryl)-phenyl] butyric acid ethyl ester, required as starting material, is produced in the following manner:

(c) 15 g. of crude 4-[(3-chloro-4-[(1-pyrryl)-phenyl]-butyric acid is dissolved in 200 ml. of ethanol and, while introducing hydrochloric acid gas, the solution is refluxed overnight. The reaction mixture is concentrated by evaporation under reduced pressure, 20 ml. of ice water are added and the mixture is adjusted to pH 9–10 with ice-cold potassium hydroxide solution. The free amino ester is extracted with 200 ml. of ether, the ether solution is dried over potash, concentrated by evaporation and the residue distilled in the bulb tube. The 4-[(4-amino-3-chlorophenyl)-butyric acid ethyl ester, a colourless oil, distills at 140° bath temperature under 0.005 torr.

(d) 14.0 g. of 4-[(4-amino-3-chlorophenyl)-butyric acid ethyl ester, 150 ml. of acetonitrile and 7.7 g. of 2,5-dimethoxymethylideneurafuran are heated to boiling. A solution of 0.4 g. of p-toluene sulphonic acid in 10 ml. of acetonitrile is then added and the solution kept boiling for 15 minutes. After evaporating off the solvent under reduced pressure, a dark residue remains. This is extracted with 300 ml. of ether, the ether solution is washed with 15 ml. of 10% potassium bicarbonate solution, dried over magnesium sulphate and concentrated by evaporation. The obtained 4-[(3-chloro-4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester distills at 140–145°/0.005 torr; nD²⁰=1.551.

The 4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester necessary as starting material for Example 6(a) may also be obtained as follows:

1.4 g. of 2-[(1-pyrryl)-phenyl]-acetooxycetic acid ethyl ester (cp. Example 14(a)) is refluxed for 16 hours with a solution of 0.11 g. sodium in 30 ml. absolute ethanol. The solution is neutralised with glacial acetic acid and evaporated under reduced pressure. The residue is dissolved in 30 ml. ether, the solution washed with 5 ml. water, dried over magnesium sulphate and concentrated. The remaining oil is distilled in a bulb tube at 130°/0.002 torr. 4-[(1-pyrryl)-phenyl]-butyric acid ethyl ester nD²⁰=1.535 is obtained.

**EXAMPLE 7**

2.95 g. of 4-[(1-pyrryl)-phenyl]-butyric acid are dissolved in 13 ml. of 1 N sodium hydroxide solution. The solution is filtered and concentrated by evaporation in the water-jet vacuum. The residue is recrystallised from methanol. The sodium salt of the 4-[(1-pyrryl)-phenyl]-butyric acid, M.P. 263–267°, is thus obtained.

**EXAMPLE 8**

1.5 g. of [1-[(1-pyrryl)-phenyl]-malonic acid diethyl ester, 20 ml. of 30% potassium hydroxide solution and 15 ml. of ethanol are refluxed for 6 hours. The solution is concentrated in the water-jet vacuum, the residue dissolved in 20 ml. of water and extracted with 10 ml. of ether. The aqueous phase is separated and adjusted to pH 1–2 with concentrated hydrochloric acid. The precipitated crystals are filtered with suction, washed twice with water using 5 ml. each time and are then dried in a desiccator over concentrated sulphuric acid. The crude 4-[(1-pyrryl)-phenyl]-malonic acid melts at 170–174° with an intense evolution of gas. The thus obtained crude acid is gradually heated with 50 mg. of copper powder to 180°, until no further evolution of gas is observed (ca. 10 minutes). The acid is extracted with 50 ml. of ether from the reaction residue. The ether is evaporated and the residue distilled in a bulb tube at 180–200° bath temperature/0.005 torr, to obtain pure 4-[(1-pyrryl)-phenyl]-butyric acid, M.P. 113–114°.

The substituted malonic ester, required as starting material, is produced in the following manner:

(a) p-nitro-phenethyil bromide is reduced with stannous chloride to the p-amino-phenethyl bromide hydrochloride, M.P. 195–200°.

(b) The base is liberated from 3.5 g. of p-amino-phenethyl bromide hydrochloride using concentrated potassium hydroxide solution, it is extracted with ether and dried over magnesium sulphate. The crude p-amino-phenethyl bromide (2.7 g.), which remains after distilling off the ether in a water-jet vacuum at 30° bath temperature, is refluxed with 30 ml. of glacial acetic acid and 1.8 g. of 2,5-dimethoxymethylideneurafuran for 15 minutes in an oil bath preheated to 130°. The reac-
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A quantity of 12.0 g. of zinc wool is shaken for 5 minutes with a solution of 0.9 g. of mercury(II)-chloride in 0.6 ml. of concentrated hydrochloric acid and 15 ml. of water. The solution is decanted and to the amalgamated zinc are added, 7.5 ml. of water, 17.5 ml. of concentrated hydrochloric acid, 10 ml. of toluene and 3.0 g. of 3-[p-(1-pyrrol)-benzoyl]-propionic acid (Example 4). The reaction mixture is refluxed whilst vigorously boiling in a bath at 150°. After 3 hours and after 6 hours are added, each time, 5 ml. of concentrated hydrochloric acid through the condenser. After 7 hours, the reaction mixture is cooled and extracted with ca. 100 ml. of chloroform. The organic phase is separated, washed twice with each time, 15 ml. of water, dried over sodium sulphate and concentrated by evaporation. The obtained red-brown oil is distilled in a bulb tube under 0.01 torr with a furnace temperature of 160–180°. The 4-[p-(1-pyrrol)-phenyl]-butyric acid is obtained as a yellowish oil which crystallises spontaneously. After recrystallisation from ligroin/ether and from isopropanol, and subsequent sublimation, the acid melts at 113–114°.

In an analogous manner using 2.5 g. 3-[3-chloro-4-(1-pyrrol)-benzoyl]-propionic acid is obtained the 4-[3-chloro-4-(1-pyrrol)-phenyl]-butyric acid, M.P. 28–60° (from isopropanol).

EXAMPLE 14

0.7 g. of crude 2-[p-(1-pyrrol)-phenethyl]-acetoacetic acid ethyl ester and 20 ml. of 50% potassium hydroxide solution are stirred for 6 hours at 120°. The reaction mixture is then diluted with 30 ml. of water and extracted with 50 ml. of ether. The aqueous phase is separated, filtered and adjusted with concentrated hydrochloric acid to pH 1–2. The precipitated acid is extracted with 50 ml. of ether, the ether extract is washed with 10 ml. of water, dried and concentrated by evaporation. The obtained crystalline residue is distilled in a bulb tube at 160–180°/0.001 torr. The obtained 4-[p-(1-pyrrol)-phenyl]-butyric acid melts at 113–114° after recrystallisation from isopropanol. The substituted acetoacetic acid ethyl ester, required as starting material, is produced in the following manner:

(a) A quantity of 0.68 g. of sodium hydride dispersion (50% in mineral oil) is added to 1.6 g. of acetoacetic acid ethyl ester, dissolved in 30 ml. of dimethyl formamide. The solution is stirred at room temperature for 20 minutes and is then stirred with a solution of 2.5 g. of p-(1-pyrrol)-phenethyl formamide (Example 18) in 10 ml. of methanol for 18 hours at 100°. The reaction mixture is then cooled, neutralised with glacial acetic acid and concentrated by evaporation under 12 torr. The residue is dissolved in 100 ml. of ether, the solution then being washed with 50 ml. of water, dried over magnesium sulphate and concentrated by evaporation. The fraction boiling at 130° bath temperature under 0.003 torr, in the form of a yellowish oil, contains the 2-[p-(1-pyrrol)-phenethyl]-acetoacetic acid ethyl ester, which is hydrolysed without further purification.

EXAMPLE 15

Analogously to Example 14, 1.6 g. of 2-[3-chloro-4-(1-pyrrol)-phenethyl]-acetoacetic acid ethyl ester are hydrolysed with 40 ml. of 50% potassium hydroxide solution for 5 hours at 100° to yield the 4-[3-chloro-4-(1-pyrrol)-phenyl]-butyric acid, M.P. 58–60° (from methanol/water/).

The 2-[3-chloro-4-1-(1-pyrrol)-phenethyl]-acetoacetic acid ethyl ester, required as starting material, is obtained, according to Example 14(a), as a brownish oil which boils in the bulb tube at 140–150°/0.001 torr, by the use of 7.5 g. of p-toluene sulphonic acid-[3-chloro-4-(1-pyrrol)-phenyl]-butyric acid, M.P. 105–115°, as starting material. The 4-[3-chloro-4-(1-pyrrol)-phenyl]-butyric acid is obtained by recrystallisation from methanol, the substance melts at 111–114°. Subsequent sublimation yields pure 4-[p-(1-pyrrol)-phenyl]-butyric acid as white crystals, M.P. 113–114°.

EXAMPLE 12

A mixture of 2.43 g. of 3-[p-(1-pyrrol)-benzoyl]pro- pionic acid (Example 5), 2.3 g. of potassium hydroxide, 1.8 ml. of 80% hydrazine hydrate and 12 ml. of triethylene glycol is prepared and refluxed for 90 minutes. The reflux condenser is then removed and the temperature of the reaction mixture is increased to 195°, whereas the excess hydrazine is distilled off, this temp-
The following prescriptions further illustrate the production of the various preparations:

EXAMPLE 16
1000 g. of active substance, e.g. 4-13-chloro-4-(1-pyrryl)-butyric acid, are mixed with 550 g. of lactose and 292 g. of potato starch. The mixture is moistened with an alcoholic solution of 8 g. of gelatine and is then granulated through a sieve. After drying, 60 g. of potato starch, 60 g. of talcum and 10 g. of magnesium stearate and 20 g. of highly dispersed silicon dioxide are mixed in and the mixture pressed into 10,000 tablets, each weighing 200 mg. and each containing 100 mg. of active substance. Optionally, the tablets can be provided with grooves for more accurate adjustment of the dosage.

EXAMPLE 17
200 g. of active substance, e.g. 4-[p-pyrryl]-phenyl-butyric acid, are well mixed with 16 g. of maize starch and 6 g. of highly dispersed silicon dioxide. The mixture is moistened with a solution of 2 g. of stearic acid, 6 g. of ethyl cellulose and 6 g. of stearin in ca. 70 ml. of isopropyl alcohol and is granulated through a sieve III (Ph. Helv. V). The granulate is dried for ca. 14 hours and is then put through sieve IIIa. It is then mixed with 16 g. of maize starch, 16 g. of talcum and 2 g. of magnesium stearate and the mixture is pressed into 1000 dragee cores. These are coated with a concentrated syrup of 2 g. of shellac, 7.5 g. of gum arabic, 0.15 g. of dyestuff, 2 g. of highly dispersed silicon dioxide, 25 g. of talcum and 53.35 g. of sugar and dried. The obtained dragees weigh each 360 mg. and each contain 200 mg. of active substance.

EXAMPLE 18
50.0 g. of 4-[p-(1-pyrryl)-phenyl]-butyric acid are dissolved in a mixture of 218 ml. of 1 N sodium hydroxide solution and 500 ml. of boiled, pyrogen-free water. The solution is made up to 2000 ml. with pyrogen-free water, is then filtered and used to fill 1000 ampoules each containing 2 ml., and sterilised. A 2 ml. ampoule contains 50 mg. of 4-[p-(1-pyrryl)-phenyl]-butyric acid as active substance in the form of the sodium salt.

EXAMPLE 19
50 g. of 4-[3-chloro-4-(1-pyrryl)-phenyl]-butyric acid and 1950 g. of finely ground suppository foundation substance (e.g. cocoa butter) are thoroughly mixed and then melted. From the melt, maintained homogeneous by stirring, are obtained 1000 suppositories each containing 500 mg. of active substance and each weighing 2 g.

EXAMPLE 20
60.0 g. of polyoxyethylene sorbitan monostearate, 30.0 g. of sorbitan monostearate, 150.0 g. of paraffin oil and 120.0 g. of stearyl alcohol are melted together. 50.0 g. of 4-[p-(1-pyrryl)-phenyl]-butyric acid (finely pulverised) are added and 590 ml. of water, preheated to 40°, are added to form an emulsion. The emulsion is stirred until it has cooled down to room temperature and is then filled into tubes.

What we claim is:
1. A compound of the Formula I

![Chemical Structure](image)

wherein
Z is the —CH₂ — or the —CO— group, and
R₁ is hydrogen or chloro,
and the pharmaceutically acceptable salts thereof.
2. A compound according to claim 1, wherein
Z is the —CH₃ — group, and
R₁ is hydrogen or chloro,
and the pharmaceutically acceptable salts thereof.
3. A compound according to claim 1, which is 4-[4-(1-pyrryl)-3-chlorophenyl]-butyric acid and the pharmaceutically acceptable salts thereof.
4. A compound according to claim 1, which is 4-[p-(1-pyrryl)-phenyl]-butyric acid and the pharmaceutically acceptable salts thereof.
5. A compound according to claim 1, which is 3-[p-(1-pyrryl)-benzoyl] propionic acid and the pharmaceutically acceptable salts thereof.

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