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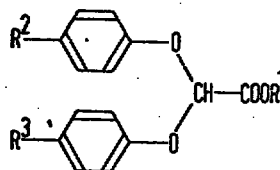


(54) DIPHENOXYACETIC ACID DERIVATIVES AND PROCESSES FOR THEIR PREPARATION

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German body corporate, of 61 Darmstadt, Frankfurter Strasse 250, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with certain novel diphenoxylacetic acid derivatives, with processes for their preparation, and with compositions containing them.

We have found that diphenoxylacetic acid derivatives of formula I:



in which R¹ is H or alkyl with 1 to 4 C atoms, R² is H or Cl, R³ is piperidino, 4-piperidinophenyl, 1,2,3,4-tetrahydroquinolino, 1-R⁴-1,2,3,4-tetrahydro-4-quinolyl, 4-oxo-1,2,3,4-tetrahydroquinolino, 4-chromanyl, 4-thiochromanyl or 4-chlorophenoxy, and R⁴ is H or alkyl with 1 to 4 C atoms, and their physiologically acceptable salts with acids or bases, are well tolerated and possess good cholesterol level-lowering activity and also triglyceride level-lowering and uric acid level-lowering activity and liver enzyme-inducing activity. (In the following text, R¹ to R⁴ have the above-stated meanings for formula I, unless expressly stated otherwise.)

Lowering of the cholesterol level can be determined, for example, in the serum of rats by the method of Levine et al. (*Automation in Analytical Chemistry*, Technicon Symposium 1967, Mediad, New York, pages 25—28), and lowering of the triglyceride level can be determined, again in the serum of rats, by the method of Noble and Campbell (*Clin. Chem.*, 16 (1970), pages 166—170). Liver-enzyme induction is shown, for example, by an increase in the weight of the liver after administering the test substance to rats for several days, and in an increase of the enzyme activities of the endoplasmatic reticulum and of other cell structures in the rat liver.

The compounds of formula I and their physiologically acceptable salts can therefore be used as medicaments and also as intermediates for the preparation of other medicaments.

The compounds of formula I and their physiologically acceptable salts are novel and constitute one aspect of the present invention.

In the compounds of formula I, when R¹ or R⁴ is alkyl, it is preferably methyl or ethyl, but may also be n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl or tert.-butyl.

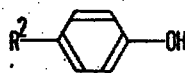
In detail, R¹ is preferably H, methyl or ethyl. R² is preferably Cl. R³ is preferably 1,2,3,4-tetrahydroquinolino or 1-methyl-1,2,3,4-tetrahydro-4-quinolyl. R⁴ is preferably H or methyl.

Particularly preferred compounds of formula I are those in which at least one of the radicals R^1 , R^2 , R^3 and/or R^4 has one of the preferred meanings stated above. Some preferred groups of compounds may be characterised by the partial formulae Ia to Ik, which correspond to formula I and wherein the radicals not defined in more detail have the meanings indicated for formula I, but wherein

- in Ia, R^1 is H, methyl or ethyl;
- in Ib, R^2 is Cl;
- in Ic, R^3 is piperidino or 4-piperidinophenyl;
- in Id, R^3 is 1,2,3,4-tetrahydroquinolino, 1- R^4 -1,2,3,4-tetrahydro-4-quinolyl or 4-oxo-1,2,3,4-tetrahydroquinolino;
- in Ie, R^3 is 1,2,3,4-tetrahydroquinolino or 1-methyl-1,2,3,4-tetrahydro-4-quinolyl;
- in If, R^3 is 4-chromanyl;
- in Ig, R^3 is 4-thiochromanyl;
- in Ih, R^3 is 4-chlorophenoxy;
- in Ii, R^4 is H or methyl;
- in Ij, R^1 is H, methyl or ethyl and R^2 is Cl;
- in Ik, R^1 is H, methyl or ethyl, R^2 is Cl and R^3 is 1,2,3-tetrahydroquinolino or 1-methyl-1,2,3,4-tetrahydro-4-quinolyl.

The present invention also comprises a process for the preparation of the novel compounds, which comprises:

(i) condensing a phenol of formula IIa or IIb:

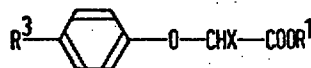


IIa

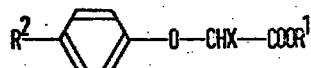


IIb

or a reactive functional derivative of such a compound, with a compound of formula IIIa or IIIb:



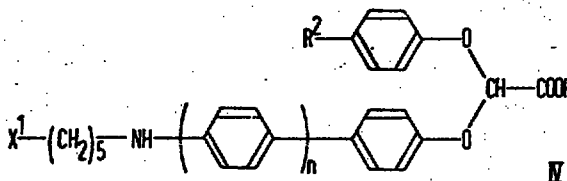
IIIa



IIIb

in which X is OH, esterified OH, Cl, Br or I, or

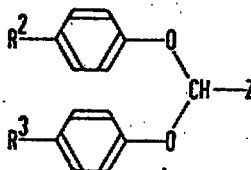
(ii) cyclising a compound of formula IV:



IV

in which X^1 is Cl, Br, I, NH_2 , OH or an esterified or etherified OH group, and n is 0 or 1; or

(iii) treating a compound of formula V:



V

in which Z is a functionally modified carboxyl group, but is different from COOR¹, with a solvolysing agent.

The compound of formula I obtained by any of these processes may, if desired, be treated with an esterifying, trans-esterifying or solvolysing agent, in order to convert the R¹ radical present therein into another R¹ radical.

The compound of formula I obtained may, if desired, be treated with an acid or base to form a physiologically acceptable salt thereof or, when a salt of a compound of formula I is obtained, the free compound of formula I may be liberated therefrom by treating the salt with a base or acid.

In the above formulae, X and X¹ are preferably Cl or Br; however, in addition to free OH and I, these radicals may also be, for example, alkylsulphonyloxy, in particular with 1 to 6 C atoms (for example, methanesulphonyloxy), arylsulphonyloxy, in particular with 6 to 10 C atoms (for example, benzenesulphonyloxy, *p*-toluenesulphonyloxy, and 1- or 2-naphthalenesulphonyloxy), or acyloxy, in particular with 1 to 7 C atoms (for example, acetoxy and benzoyloxy), and X¹ can, in addition, be NH₂ or, for example, an etherified OH group, particularly with 1 to 7 C atoms (for example, methoxy or benzyloxy).

The diphenoxyacetic acid derivatives of formula I can be prepared according to method which are in themselves known and described in the literature, preferably by reaction of a phenol of formula IIa or IIb with a compound of formula IIIa or IIIb. The phenols IIa are known and the phenols IIb are known in part. Where they are new, they can be prepared according to known methods, for example by splitting their methyl ethers (corresponding to IIb, but with OCH₃ instead of OH) by treatment with HBr. The compounds IIIa and IIIb are also known for the most part; they are obtainable by methods which are in themselves known. The phenol IIa or IIb may be converted, prior to the reaction, into a salt thereof, particularly into a metal salt, for example an alkali metal salt, preferably a Li, Na or K salt. To form the salt, the phenol may be reacted with a reagent which forms the metal salt, for example an alkali metal, such as Na, an alkali metal hydride or amide, such as LiH, NaH, NaNH₂ or KNH₂, an alkali metal lower alcoholate (that is an alcoholate derived from an alcohol containing up to 4 C atoms), such as lithium, sodium or potassium methylate, ethylate, or tert.-butylate, an organometallic compound, such as butyl-lithium, phenyl-lithium or phenyl-sodium, or a metal hydroxide, carbonate or bicarbonate, such as lithium, sodium, potassium or calcium hydroxide, carbonate or bicarbonate. The preparation of the phenolate is preferably carried out in the presence of a solvent, for example a hydrocarbon, such as hexane, benzene, toluene or xylene; an ether, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), dioxan or diethylene glycol dimethyl ether; an amide, such as dimethylformamide (DMF) or hexamethylphosphoric acid triamide (HMPT); an alcohol, such as methanol or ethanol; or a ketone, such as acetone or butanone, or a mixture of two or more of these solvents. The phenol IIa or IIb or a salt thereof is reacted with the compound IIIa or IIIb, preferably in the presence of a diluent, for example in the presence of the solvent which has been used for the preparation of the salt, but which can be replaced by another solvent or be diluted with another solvent.

The reaction is, in general, carried out at a temperature of from -20° to 150°C, preferably from 20° to 120°C and, more preferably, at the boiling point of the solvent used. It may be carried out under an inert gas, for example nitrogen. The phenolate can also be formed *in situ*; in that case, the phenol and the compound IIIa or IIIb are allowed to react with one another in the presence of the salt-forming reagent.

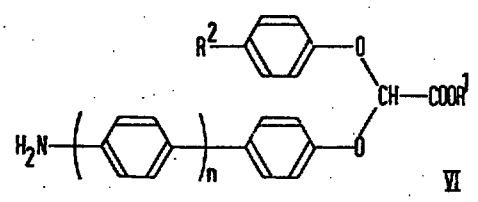
A particularly preferred method is to boil the compounds IIa or IIb and IIIa or IIIb (X=Cl or Br, R¹=CH₃ or C₂H₅) together in an alcoholic (for example, ethanolic) sodium alcoholate solution for 2 to 8 hours.

A free phenol IIa or IIb may also be reacted with a hydroxy-acid derivative IIIa or IIIb (X=OH), preferably in the presence of a condensation agent. Suitable condensation agents are, for example, acid dehydration catalysts, for example mineral acids such as sulphuric acid or phosphoric acid, and also *p*-toluenesulphonyl chloride, arsenic acid, boric acid, NaHSO₄ or KHSO₄, as well as diaryl carbonates (for example, diphenyl carbonate), dialkyl carbonates (for example, dimethyl carbonate or diethyl carbonate) or carbodiimides (for example, dicyclohexylcarbodiimide). If an acid is used as the condensation agent, the reaction is suitably carried out in an excess of the acid, without the addition of a further solvent, at a temperature of from 0° to 100°C, preferably from 50° to 60°C. However, a diluent, for example benzene, toluene or dioxan, may also be added. If a carbonic acid ester is used, the reaction is preferably carried out at a higher temperature, suitably from 100° to 210°C and preferably from

180° to 200°C; a trans-esterification catalyst, such as sodium carbonate or potassium carbonate or sodium methylate, may be added, if desired.

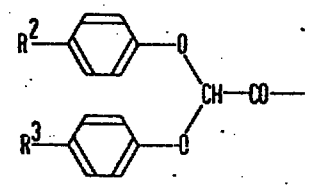
Compounds of formula IV can be cyclised according to methods described in the literature to compounds of formula I, for example by heating in the presence or absence of a solvent and, optionally, in the presence of an acidic or basic catalyst.

Compounds of formula IV can be obtained, for example, by reacting a compound of the formula $X^1-(CH_2)_5-X^1$ (in which X^1 has the above-mentioned meaning, but the two X^1 groups may be the same or different and may also together be O or NH, preferably 1,5-dibromopentane, but also, for example, 1,5-dichloropentane or 1,5-diiodopentane, piperidine, 1,5-pentanediol and its reactive esters, for example its bis-*p*-toluenesulphonate) with a compound of formula VI:



Suitable solvents for the cyclisation of IV are, for example, water, lower aliphatic alcohols (that is containing up to 4 C atoms; such as, methanol, ethanol, isopropanol and n-butanol), glycols (such as, ethylene glycol), ethers (such as, diethyl ether or diisopropyl ether, THF or dioxan), aliphatic hydrocarbons (such as, petroleum ether or hexane), or aromatic hydrocarbons (such as, benzene, toluene or xylene), halogenated hydrocarbons (such as, chloroform and chlorobenzene), nitriles (such as, acetonitrile), amides (such as, DMF or dimethylacetamide and HMPT), or sulfoxides (such as, dimethylsulphoxide) or mixtures of two or more of these solvents. Cyclisation is, in general, carried out at a temperature of from 0° to 300°C, preferably from room temperature to the boiling point of the solvent used, which can be raised by the application of pressure (up to 200 atmospheres). The choice of catalyst depends on the nature of the compound HX^1 which is to be split off. When X^1 =halogen, basic catalysts are preferred, examples being inorganic bases (alkali metal or alkaline earth metal hydroxides, carbonates or alcoholates, such as NaOH, KOH, LiOH, Ba(OH)₂, Ca(OH)₂, NaCO₃, K₂CO₃, Li₂CO₃, NaOCH₃, KOCH₃, NaOC₂H₅, KOC₂H₅, K tert.-butylate) or organic bases (for example, tertiary amines such as triethylamine, pyridine, picolines and quinoline). On the other hand, when X^1 =OH, alkoxy, acyloxy, alkylsulphonyloxy or arylsulphonyloxy, it is advisable to use acidic catalysts, for example inorganic acids (such as, sulphuric acid, polyphosphoric acid, hydrobromic acid or hydrochloric acid) and/or organic acids (such as, formic acid, acetic acid, propionic acid or *p*-toluenesulphonic acid), which, when used in excess, can at the same time also serve as solvents. In general, more vigorous conditions are required for the cyclisation of these compounds. Compounds of formula IV ($X^1=NH_2$) eliminate ammonia on heating, for example on melting, the desired compounds of formula I being produced at the same time. A preferred procedure is not to isolate the compound of formula IV but to prepare it in the nascent state (for example from VI) in the presence or absence of an additional solvent and cyclise it directly to a compound of formula I.

The diphenoxyacetic acid derivatives I can also be obtained by solvolysis (preferably hydrolysis) of other diphenoxyacetic acid derivatives of formula V. In these, Z is, in particular, one of the following radicals (wherein the R' and R'' groups which are to be split off may be of any desired kind and are, for example, each alkyl with, preferably, 1 to 4 C atoms, which may be the same or different, or may together be, for example, tetramethylene or pentamethylene, optionally interrupted by O); CHAl₃; COOR''' (wherein R''' is a radical different from R¹, particularly alkyl with 5 to 12 C atoms or an alkyl radical substituted in any desired manner); C(OR')₃; COOAcyl (wherein Acyl is the radical of a carboxylic acid with up to 25 C atoms, preferably an acyl radical of the formula



corresponding to the d-phenoxyacetic acid I); CN; CONH₂; CONHR'; CONR'R''; CONHOH; C(OH)=NOH; CONHNH₂; CON₃; C(OR')=NH; C(NH₂)=NNH₂; C(NHNH₂)=NH; CSH; COSH; CSOR'; CSNH₂; CSNHR' or CSNR'R''. Z is preferably a nitrile or acid amide group. The compounds V are obtainable, for example, by reaction of a phenol IIa or IIb with a compound corresponding to formula IIIa or IIb, but with Z in place of COOR¹, in accordance with the above-mentioned methods.

Hydrolysis of compounds of formula V may be carried out in an acidic or alkaline medium at a temperature of from -20° to 300°C, preferably at the boiling point of the solvent used. Examples of suitable acidic catalysts are hydrochloric acid, sulphuric acid, phosphoric acid or hydrobromic acid; examples of suitable basic catalysts are sodium, potassium or calcium hydroxide, sodium carbonate or potassium carbonate. Suitable solvents are, for example, water, lower alcohols such as methanol or ethanol, ethers such as THF or dioxan, amides such as DMF, nitriles such as acetonitrile, sulphones such as tetramethylenesulphone or mixtures of two or more of these solvents, particularly mixtures containing water. The preferred hydrolysis of nitriles (V, Z=CN) or acid amides (V, Z=CONH₂, CONHR' or CONR'R'') is suitably carried out in an acidic medium (for example with acetic acid/hydrochloric acid) or an alkaline medium (for example with alcoholic alkali).

Using solvolytic methods, esters of formula I (R¹=alkyl with 1 to 4 C atoms) can be prepared. For example, the nitriles V (Z=CN) can be converted, by reaction with alcoholic hydrochloric acid, into the corresponding iminoalkyl-ether hydrochlorides, and these can be converted into the corresponding alkyl esters by partial hydrolysis.

If desired, the R¹ radical in a resulting compound of formula I can be converted into another R¹ radical by esterification, trans-esterification or solvolysis in accordance with methods described in the literature.

For example, an acid of formula I (R¹=H) can be esterified with an alkanol having 1 to 4 C atoms, suitably in the presence of an inorganic or organic acid, such as HCl, HBr, HI, H₂SO₄, H₃PO₄, trifluoroacetic acid, benzenesulphonic acid or p-toluenesulphonic acid or in the presence of an acidic ion exchanger, and optionally in the presence of an inert solvent, such as benzene, toluene or xylene, at a temperature of from 0° to, preferably, the boiling point of the reaction mixture. The alcohol is preferably employed in excess. Such esters can also be obtained by addition reaction of the carboxylic acids I (R¹=H) with olefins (for example, isobutylene), or by reaction of the carboxylic acids with diazoalkanes, for example diazomethane. Furthermore, the esters can be prepared by reaction of metal salts of the acids I (R¹=H), preferably the alkali metal salts, lead salts or silver salts, with alkyl halides or alkyl chlorosulphites, the resulting adducts subsequently being thermally decomposed. The esterification can also be carried out in several stages. For example, the corresponding acid halide, for example the acid chloride, may first be prepared from the acid I (R¹=H) and the acid halide is then reacted with the alcohol, if appropriate in the presence of an acidic or basic catalyst.

Esters of formula I (R¹=alkyl with 1 to 4 C atoms) can also be obtained by trans-esterification, especially by reaction of other esters with an excess of the appropriate alcohol, or by reaction of the carboxylic acids I (R¹=H) with any other desired esters of the appropriate alcohol (preferably alkanoates, wherein the alkanoyl radical has up to 4 C atoms), the reaction preferably being carried out in the presence of basic or acidic catalysts, for example sodium ethylate or sulphuric acid, and at a temperature of from 0° to, preferably, the boiling point of the reaction mixture.

The R¹ radical in a compound of formula I can also be converted into another R¹ radical by treatment with solvolysing agents and, in particular, to saponify an ester to the corresponding acid I (R¹=H). The solvolysis or saponification can be carried out according to any one of the methods indicated above for the solvolysis of the compounds of formula V. Such esters are preferably saponified by treatment with alcoholic alkali solutions, for example, ethanolic potassium hydroxide, at a temperature of from 20 to 120°C, preferably at the boiling point of the reaction mixture.

A basic compound of formula I can be converted to an acid addition salt thereof by reaction with an acid. Acids which give physiologically acceptable salts should be used for this purpose. Both organic and inorganic acids are suitable, examples being aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic acids or sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, aminocarboxylic acids, sulphamic acid, benzoic acid, salicylic acid, phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic acid, ethanedisulphonic acid, 2-

hydroxyethanesulphonic acid, *p*-toluenesulphonic acid, naphthalenemonosulphonic acids and naphthalenedisulphonic acids, sulphuric acid, nitric acid, hydrogen halide acids, such as hydrochloric acid or hydrobromic acid, or phosphoric acids, such as orthophosphoric acid.

5 On the other hand, acids of formula I ($R^1=H$) can be converted into one of their physiologically acceptable metal salts or ammonium salts by reaction with a base. Suitable salts are, in particular, the sodium, potassium, magnesium, calcium and ammonium salts, and also substituted ammonium salts, such as, for example, the dimethylammonium, diethylammonium, diisopropylammonium, monoethanolammonium, diethanolammonium and triethanolammonium, cyclohexylammonium, dicyclohexylammonium and dibenzylethylenediammonium salts.

10 Conversely, compounds of formula I can be liberated from their acid addition salts by treatment with strong bases, or from their metal salts and ammonium salts by treatment with acids.

15 The compounds of formula I contain a centre of asymmetry and are usually obtained in the racemic form. The racemates can be separated into their optical antipodes by the use of known methods, such as are described in the literature, for example by reaction with optically active bases or acids. Furthermore, optically active compounds can be obtained by the methods described, by using starting materials which are already optically active.

20 The novel compounds according to the invention are used in human and veterinary medicine in admixture with solid, liquid and/or semi-liquid inert, physiologically acceptable carriers or excipients. Suitable carriers are organic or inorganic substances which are suitable for parenteral, enteral or topical administration and which do not react with the new compounds, such as, for example, water, vegetable oils, benzyl alcohol, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talc, white petroleum jelly and cholesterol. Compositions for parenteral administration preferably take the form of solutions, preferably oily or aqueous solutions, or suspensions, emulsions or implants. Compositions in the form of tablets, dragées, capsules, syrups, elixirs or suppositories are suitable for enteral administration and ointments, creams or powders are suitable for topical use. Such compositions may optionally be sterilised and/or contain additives, such as lubricants, preservatives, stabilisers or wetting agents, emulsifiers, salts for regulating the osmotic pressure, buffer substances, dyestuffs, flavouring substances and/or aromatic essences.

25 The novel compounds according to the invention are, in general, administered analogously to the known compound Clofibrate, preferably in daily dosages of from 0.5 to 20 mg/kg of body weight. Oral administration is preferred. When compositions are formulated in dosage unit form, each dosage unit preferably contains from 10 to 1000, more preferably 20 to 500, mg of the active compound per dosage unit.

30 In order that the invention may be more fully understood, the following examples are given by way of illustration only.

35 In the examples, all temperatures are in °C. Reference in the examples to "standard working up" means that the reaction mixture was cooled and evaporated, water was added, the mixture was extracted with ether, the ethereal extract was washed with aqueous sodium bicarbonate solution and with water, and dried over Na_2SO_4 , the ether was distilled off and the crude product was purified by distillation or crystallisation, where appropriate by crystallisation of an acid addition salt.

Example 1

40 a) 2.3 g of sodium were dissolved in 200 ml of absolute ethanol. 25.3 g of 4-(4-piperidinophenyl)-phenol, followed by 29.4 g of α -bromo- α -(4-chlorophenoxy)-acetic acid ethyl ester, were added whilst stirring, and the mixture was boiled for 5 hours. It was then cooled, the product was filtered off and washed with water, and 4-chlorophenoxy)-[4-(4-piperidinophenyl)-phenoxy]-acetic acid ethyl ester, m.p. 107—108° (from ethyl acetate/hexane) was obtained.

45 Analogously, 4-piperidinophenol, 4-(1,2,3,4-tetrahydroquinolino)-phenol, 4-(1,2,3,4-tetrahydro-4-quinolyl)-phenol, 4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenol, 4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenol, 4-(4-chromanyl)-phenol, 4-(4-thiochromanyl)-phenol and 4-(4-chlorophenoxy)-phenol gave:

50 (4-Chlorophenoxy)-(4-piperidinophenoxy)-acetic acid ethyl ester;
(4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester;
55 (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid ethyl ester;

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- (4-chlorophenoxy)-[4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid ethyl ester, oil; n_D^{20} 1.5700;
(4-chlorophenoxy)-[4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester, m.p. 122—123°;
5 (4-chlorophenoxy)-[4-(4-chromanyl)-phenoxy]-acetic acid ethyl ester, oil; n_D^{20} 1.5808;
(4-chlorophenoxy)-[4-(4-thiochromanyl)-phenoxy]-acetic acid ethyl ester; and
(4-chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetic acid ethyl ester, oil; n_D^{20} 1.5796.
- 10 b) 4.64 g of (4-chlorophenoxy)-[4-(4-piperidinophenyl)-phenoxy]-acetic acid ethyl ester were boiled with 1 g of KOH in 25 ml of ethanol for 2½ hours. The mixture was evaporated, water was added, the solution was washed with ether and hydrochloric acid was added until the pH was 5. The resulting (4-chlorophenoxy)-[4-(4-piperidinophenyl)-phenoxy]-acetic acid was filtered off.
- 15 The following were obtained analogously by saponification of the corresponding ethyl esters:
- (4-Chlorophenoxy)-(4-piperidinophenoxy)-acetic acid, diisopropylamine salt, m.p. 148—150°;
20 (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid, diisopropylamine salt, m.p. 129—132°;
(4-chlorophenoxy)-[4-(1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid;
(4-chlorophenoxy)-[4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid, diisopropylamine salt, m.p. 152—155°;
25 (4-chlorophenoxy)-[4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid;
(4-chlorophenoxy)-[4-(4-chromanyl)-phenoxy]-acetic acid;
(4-chlorophenoxy)-[4-(4-thiochromanyl)-phenoxy]-acetic acid; and
(4-chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetic acid, m.p. 122—123°; cyclohexylamine salt, m.p. 130°.
- Example 2
- 30 a) 17.7 g of 4-piperidinophenol were added to a suspension of 2.4 g of NaH in 200 ml of dimethylacetamide. The mixture was stirred for one hour at 20° and then heated to 100°, 25.9 g of α -bromo- α -phenoxyacetic acid ethyl ester were added, the mixture was heated to 160° for 16 hours and after standard working up, phenoxy-(4-piperidinophenoxy)-acetic acid ethyl ester was obtained.
- 35 Analogously, the following were obtained using the corresponding phenols:
- Phenoxy-[4-(4-piperidinophenyl)-phenoxy]-acetic acid ethyl ester,
phenoxy-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester,
phenoxy-[4-(1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid ethyl ester,
40 phenoxy-[4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid ethyl ester,
phenoxy-[4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester,
phenoxy-[4-(4-chromanyl)-phenoxy]-acetic acid ethyl ester,
phenoxy-[4-(4-thiochromanyl)-phenoxy]-acetic acid ethyl ester, and
phenoxy-[4-(4-chlorophenoxy)-phenoxy]-acetic acid ethyl ester.
- 45 b) 3.55 g of phenoxy-(4-piperidinophenoxy)-acetic acid ethyl ester were boiled with 1 g of NaOH in 40 ml of methanol for 4 hours. The mixture was evaporated, water was added to the residue, this mixture was washed with ether, hydrochloric acid was added until the pH reached 5, and phenoxy-(4-piperidinophenoxy)-acetic acid was obtained.
- 50 Analogously, the following were obtained by saponification of the corresponding ethyl esters:
- Phenoxy-[4-(4-piperidinophenyl)-phenoxy]-acetic acid,
phenoxy-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid,
phenoxy-[4-(1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid,
55 phenoxy-[4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid,
phenoxy-[4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid,
phenoxy-[4-(4-chromanyl)-phenoxy]-acetic acid,
phenoxy-[4-(4-thiochromanyl)-phenoxy]-acetic acid, and
phenoxy-[4-(4-chlorophenoxy)-phenoxy]-acetic acid.

Example 3

A mixture of 1.29 g of 4-chlorophenol and 0.23 g of sodium in 60 ml of xylene was boiled for 3 hours. It was then allowed to cool to 20°, 3.9 g of α -bromo- α -(4-(1,2,3,4-tetrahydroquinolino)-phenoxy)-acetic acid ethyl ester in 30 ml of xylene were added and the suspension was stirred for 6 hours at the boil, cooled and treated with 2 ml of ethanol. The inorganic precipitate was filtered off, the filtrate was evaporated, the residue was taken up in ether, and the solution was washed with NaHCO₃ solution and saturated NaCl solution, dried over MgSO₄ and evaporated. (4-Chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester was obtained.

Analogously, reaction of the phenols mentioned in Example 1 with α -bromo- α -(4-chlorophenoxy)-acetic acid methyl ester, α -bromo- α -(4-chlorophenoxy)-acetic acid n-propyl ester, α -bromo- α -(4-chlorophenoxy)-acetic acid isopropyl ester, α -bromo- α -(4-chlorophenoxy)-acetic acid n-butyl ester, α -bromo- α -(4-chlorophenoxy)-acetic acid isobutyl ester, α -bromo- α -(4-chlorophenoxy)-acetic acid sec.-butyl ester and α -bromo- α -(4-chlorophenoxy)-acetic acid tert.-butyl ester gave the corresponding esters of the acids mentioned in Example 1b), for example (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid methyl ester, n-propyl ester, isopropyl ester, n-butyl ester, isobutyl ester, sec.-butyl ester and tert.-butyl ester.

Example 4

A solution 23.9 g of α -chloro- α -(4-chlorophenoxy)-acetic acid ethyl ester in 60 ml of acetone was added slowly to a stirred mixture of 23.9 g of 4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenol, 6.9 g of K₂CO₃ and 80 ml of acetone. The mixture was boiled for 12 hours whilst stirring, then filtered and after standard working up, (4-chlorophenoxy)-[4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester, m.p. 122—123°, was obtained.

Example 5

15 g of sulphuric acid were added to a mixture of 22 g of 4-(4-chlorophenoxy)-phenol and 23 g of 4-chlorophenoxy-glycolic acid ethyl ester (obtainable by selective hydrolysis of 4-chlorophenoxy-bromoacetic acid ethyl ester with water) and the reaction mixture was stirred for 2 hours at 50—60°. After cooling, it was mixed with water, dilute NaOH was added until the pH was 8, and the aqueous phase extracted with ether. The extract was dried and evaporated, and (4-chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetic acid ethyl ester was obtained as an oil, n_D^{20} 1.5796.

Example 6

a) 17.7 g of 4-piperidinophenol were dissolved in 100 ml of acetone. 4 g of NaOH were added whilst stirring, and thereafter 26.5 g of α -bromo- α -(4-chlorophenoxy)-acetic acid in 60 ml of acetone were added dropwise whilst stirring and boiling the mixture; the mixture was then stirred additionally for one hour at 56° and left to stand for 24 hours. The acetone was distilled off, the residue was dissolved in 1 litre of water and the solution was repeatedly washed with ether and acidified with HCl to pH 5. The (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid which precipitated was converted to the diisopropylamine salt (m.p. 148—150°).

The acids indicated in Example 1b) and 2b) were obtained analogously from the phenols mentioned in Example 1a).

b) 1 g of (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid was dissolved in 20 ml of ether and a solution of diazomethane in ether was added dropwise until a yellow colouration persisted. After evaporation, (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid-methyl ester was obtained.

The remaining acids mentioned in Example 1b) and 2b) gave the corresponding methyl esters analogously.

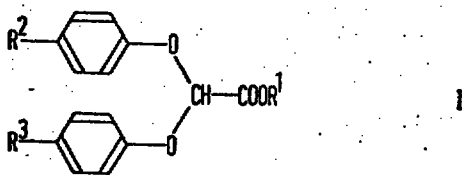
b) 5 g of (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid were dissolved in 200 ml of saturated ethanolic hydrochloric acid, and the solution was left to stand for 12 hours at room temperature, boiled for 2 hours and then evaporated. The residue was dissolved in water and the aqueous solution was adjusted to pH 8 with 1 N NaOH and extracted with ethyl acetate. The extract was dried and evaporated and (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid ethyl ester was obtained.

Analogously, the acids indicated in Example 1b) and 2b) gave, with ethanolic hydrochloric acid, the corresponding ethyl esters, mentioned in Example 1a) and 2a). If instead of ethanol other alcohols were used, the corresponding esters were obtained; for example, n-butanol gave (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid n-butyl ester.

9	1,437,300	9
	Example 7	
5	2.3 g of 1,5-dibromopentane, 3.2 g of (4-chlorophenoxy)-(4-aminophenoxy)-acetic acid ethyl ester [obtainable by reaction of Na 4-nitrophenolate with α -bromo- α -(4-chlorophenoxy)-acetic acid ethyl ester to give (4-chlorophenoxy)-(4-nitrophenoxy)-acetic acid ethyl ester, and subsequent hydrogenation] and 1.4 g of K_2CO_3 in 40 ml of n-butanol were boiled for 12 hours. (4-Chlorophenoxy)-[4-(5-bromopentylamino)-phenoxy]-acetic acid ethyl ester was formed transiently. After standard working up, (4-chlorophenoxy)-(4-piperidinophenoxy)-acetic acid ethyl ester was obtained.	5
10	Analogously, (4-chlorophenoxy) - [4 - (p - 5 - bromopentylaminophenyl) - phenoxy]-acetic acid ethyl ester gave (4-chlorophenoxy)-[4-(4-piperidinophenyl)-phenoxy]-acetic acid ethyl ester, m.p. 107—108°.	10
	Example 8	
15	2 g of (4-chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetonitrile (obtainable from 4-(4-chlorophenoxy)-phenol and α -bromo- α -4-chlorophenoxyacetonitrile) were boiled with 2 g of KOH in 20 ml of ethanol and 2 ml of water for 40 hours. The mixture was evaporated, the residue was mixed with water and extracted with ether, hydrochloric acid was added until the pH reached 5, and (4-chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetic acid was obtained.	15
20	Analogously, alkaline hydrolysis of the appropriate nitriles gave the carboxylic acids indicated in Example 1b) and 2b).	20
	Example 9	
25	1 g of (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetonitrile was boiled with 6 ml of acetic acid and 6 ml of concentrated hydrochloric acid for 2 hours under nitrogen. The mixture was evaporated, the residue was dissolved in dilute NaOH, the solution was extracted with ether, hydrochloric acid was added until the pH reached 5, and (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid was obtained, diisopropylamine salt m.p. 129—132°C.	25
30	The carboxylic acids mentioned in Example 1b) and 2b) were obtained analogously by acid hydrolysis of the corresponding nitriles.	30
	Example 10	
35	3 g of (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetamide (obtainable from 4-(1,2,3,4-tetrahydroquinolino)-phenol and α -bromo- α -(4-chlorophenoxy)-acetamide) and 5 g of KOH in 100 ml of ethanol were boiled for 3 hours under nitrogen. The mixture was evaporated, The residue was mixed with water and extracted with ether, hydrochloric acid was added until the pH reached 4, and (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid, diisopropylamine salt, m.p. 129—132°, was obtained.	35
40	The carboxylic acids mentioned in Example 1b) and 2b) were obtained analogously by alkaline hydrolysis of the corresponding amides.	40
	Example 11	
45	10 g of (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetyl chloride (obtainable from the acid and $SOCl_2$) and 100 ml of absolute n-propanol were warmed to 95° for 3 hours. The mixture was evaporated, dilute sodium hydroxide solution was added to the residue and the aqueous solution was extracted with ether. The ether solution was washed twice with dilute NaOH and twice with water and was dried; the ether was evaporated off and (4-chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid n-propyl ester was obtained.	45
50	The following examples of pharmaceutical compositions containing a compound according to the invention, are given by way of illustration.	50
	Example A: tablets	
55	A mixture of 10 kg of the diisopropylamine salt of (4-chlorophenoxy)-[4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid, 40 kg of lactose, 12 kg of wheat starch, 2 kg of talc and 1 kg of magnesium stearate was pressed in the usual manner to form tablets, each tablet containing 100 mg of the active compound.	55
	Example B: dragées	
60	Dragée cores were pressed as described in Example A and were then provided with a coating which consisted of sugar, maize starch, talc and tragacanth. Tablets and dragées which contained one or more of the other active compounds of formula I or their physiologically acceptable salts were obtainable analogously.	60

WHAT WE CLAIM IS:—

1. Diphenoxyacetic acid derivatives of formula I:



in which R¹ is H or alkyl with 1 to 4 C atoms, R² is H or Cl, R³ is piperidino, 4-piperidinophenyl, 1,2,3,4-tetrahydroquinolino, 1-R⁴-1,2,3,4-tetrahydro-4-quinolyl, 4-oxo-1,2,3,4-tetrahydroquinolino, 4-chromanyl, 4-thiochromanyl or 4-chlorophenoxy, and R⁴ is H or alkyl with 1 to 4 C atoms, and their physiologically acceptable salts with acids or bases.

2. (4-Chlorophenoxy)-(4-piperidinophenoxy)-acetic acid.

3. (4-Chlorophenoxy)-[4-(4-piperidinophenyl)-phenoxy]-acetic acid ethyl ester.

4. (4-Chlorophenoxy)-[4-(1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid.

5. (4-Chlorophenoxy)-[4-(1-methyl-1,2,3,4-tetrahydro-4-quinolyl)-phenoxy]-acetic acid.

6. (4-Chlorophenoxy)-[4-(4-oxo-1,2,3,4-tetrahydroquinolino)-phenoxy]-acetic acid ethyl ester.

7. (4-Chlorophenoxy)-[4-(4-chromanyl)-phenoxy]-acetic acid ethyl ester.

8. (4-Chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetic acid.

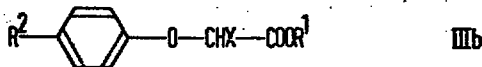
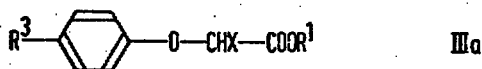
9. (4-Chlorophenoxy)-[4-(4-chlorophenoxy)-phenoxy]-acetic acid ethyl ester.

10. A physiologically acceptable salt of the compound claimed in any of claims 2 to 9.

11. A process for the preparation of a diphenoxyacetic acid derivative of formula I specified in claim 1, which comprises condensing a phenol of formula IIa or IIb:

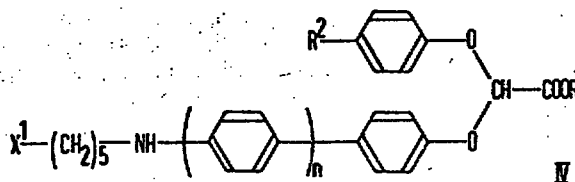


in which R² and R³ have the meanings specified in claim 1, or a reactive functional derivative of such a compound, with a compound of formula IIIa or IIIb:



in which X is OH, esterified OH, Cl, Br or I, and R¹, R² and R³ have the meanings specified in claim 1.

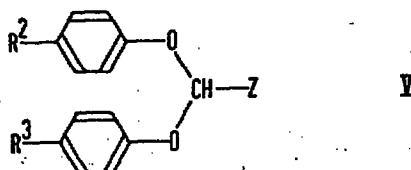
12. A process for the preparation of a diphenoxyacetic acid derivative of formula I specified in claim 1, which comprises cyclising a compound of formula IV:



in which X¹ is Cl, Br, I, NH₂, OH or an esterified or etherified OH group, n is 0 or 1, and R¹ and R² have the meanings specified in claim 1.



13. A process for the preparation of a diphenoxyacetic acid derivative of formula I specified in claim 1, which comprises treating a compound of formula V:



in which Z is a functionally modified carboxyl group, but is different from COOR¹, and R¹, R² and R³ have the meanings specified in claim 1, with a solvolysing agent.

14. A process according to any of claims 11 to 13, in which the compound of formula I obtained is treated with an esterifying, transesterifying or solvolysing agent to convert the R¹ radical present therein, into another R¹ radical.

15. A process according to any of claims 11 to 14, in which the compound of formula I obtained is treated with an acid or base in order to obtain a physiologically acceptable salt thereof or, when a salt of a compound of formula I is obtained, the salt is treated with a base or acid to liberate the compound of formula I therefrom.

16. A process for the preparation of a diphenoxyacetic acid derivative of formula I substantially as herein described in any of Examples 1 to 11.

17. A pharmaceutical composition a diphenoxyacetic acid derivative according to any of claims 1 to 10, and an inert, physiologically acceptable carrier.

18. A pharmaceutical composition according to claim 17 in dosage unit form, each dosage unit containing from 10 to 1000 mg of said compound.

19. A pharmaceutical composition according to claim 17 substantially as herein described in either Example A or B.

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