

PATENT SPECIFICATION

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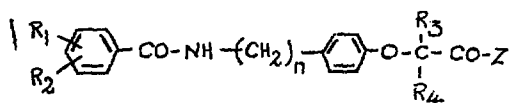


(54) NEW PHENOXY-ALKYL-CARBOXYLIC ACID DERIVATIVES AND THE PREPARATION THEREOF

(71) We, BOEHRINGER MANNHEIM G.M.B.H., of Mannheim-Waldhof, Germany, a Body Corporate organised under the laws of 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:—

10 The present invention is concerned with new phenoxy - alkyl - carboxylic acid derivatives and with the preparation thereof.

15 The new phenoxy - alkyl - carboxylic acid derivatives according to the present invention are compounds of the general formula:—

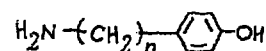


20 wherein R_1 and R_2 , which may be the same or different, are hydrogen or halogen atoms or alkyl or alkoxy radicals containing up to 5 carbon atoms, R_3 and R_4 , which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 5 carbon atoms, n is 1, 2 or 3 and Z is a hydroxyl group or an alkoxy radical containing up to 5 carbon atoms; and the pharmacologically compatible salts thereof.

25 The new compounds (I) according to the present invention show, in animal experiments, a considerable lowering of the serum lipid level and of the cholesterol level, without undesirable side effects occurring. Therefore, the new compounds (I) according to the present invention are effective agents against atherosclerosis.

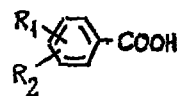
35 The new compounds according to the pre-

sent invention can be prepared, for example, by reacting an amine of the general formula:—



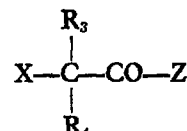
(II)

wherein n has the same meaning as above, optionally after introduction of a conventional protective group for the amino or hydroxyl group which is to be temporarily protected, with a derivative of an acid of the general formula:—



(III)

wherein R_1 and R_2 have the same meanings as above, and with a compound of the general formula:—



(IV) 50

wherein R_3 , R_4 and Z have the same meanings as above and X is a halogen atom or the residue of a sulphonic acid, whereafter the compounds obtained are, if desired, converted into their pharmacologically compatible salts. 55

[Price 25p]

The substituents R₁, R₂ and Z can, subsequent to the condensation reaction to give the fundamental structure, either be introduced or changed in known manner.

5 The condensation of the compounds of general formula (II) with the compounds of general formulae (III) and (IV) is preferably carried out by intermediate blocking of one of the two reactive groups in the compound
10 (II) with a protective group which can easily be split off and is conventionally used for this purpose, reaction with a compound of general formula (III) or (IV), splitting off of the protective groups and reaction with the
15 second compound of general formula (III) or (IV).

As reactive derivatives of the compounds (III), it is especially preferred to use halides, anhydrides or imidazolides of the appropriately substituted benzoic acids which can be reacted, for example, under the conditions of the Schotten-Baumann reaction, i.e. with the addition of a tertiary amine, for example, pyridine or dimethylaniline, in an inert solvent, with the compounds of general formula
25 (II). As inert solvent, it is preferred to use an excess of the tertiary amine. It is also preferred temporarily to block the phenolic hydroxyl group by esterification but a blocking of the phenolic hydroxyl group by
30 etherification with a compound of general formula (IV) is especially preferred.

For a primary reaction of compounds (II) with compounds (IV), it is advantageous first to convert the amino group of the compound
35 (II) into a phthalimide group which, after reaction with, for example, hydrazine or hydroxylamine, can again easily be split off in known manner. Furthermore, the reaction
40 can be promoted by converting the phenolic hydroxyl group of the compound (II) into a phenolate, for example, by reaction with a sodium alcoholate. The reaction of both components is carried out in inert solvents, for
45 example in toluene or xylene, preferably at an elevated temperature.

The compounds (I) can, if desired, be converted into their pharmacologically compatible salts by reaction with a non-toxic
50 inorganic or organic acid.

The present invention also includes pharmaceutical compositions containing at least one of the new compounds of general
55 formula (I), in admixture with a solid or liquid pharmaceutical diluent or carrier.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1.

60 Ethyl α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyrate.

41.0 g. (292 mMol) benzoyl chloride are added dropwise, in the course of 10 minutes, to 20.1 g. (146 mMol) tyramine in 60 ml.

anhydrous pyridine, while stirring and with the exclusion of moisture, and then rinsed with about 50 ml. anhydrous pyridine. The solution, which automatically warms up on adding the benzoyl chloride, is subsequently heated to 100°C. for 15 minutes in order to complete the reaction, then cooled to 35°C. and poured into a mixture of about 500 g. ice and water. The resultant crystalline slurry is acidified with dilute hydrochloric acid, filtered off with suction, washed with dilute hydrochloric acid, water and aqueous sodium bicarbonate solution and dried. After recrystallisation from acetone, there are obtained 38.3 g. (76% of theory) dibenzoyl - tyramine, which has a melting point of 173—174°C. From the mother liquors, there can be obtained a further 9.9 g. of product, so that the total yield is more than 90% of theory.

38.0 g. (0.11 mol) dibenzoyl - tyramine are suspended in 400 ml. methanol, 130 ml. 2N aqueous potassium hydroxide solution are added thereto and the mixture is heated for 1 hour at 40—45°C. After cooling, 130 ml. 2N hydrochloric acid are added. The precipitate which is formed is filtered off with suction, the filtrate is freed from methanol in a vacuum and the precipitate thereby obtained combined with that from the hydrochloric acid precipitation. The precipitates are washed with water and, for the removal of any benzoic acid which may be present, digested with an aqueous solution of sodium bicarbonate. After recrystallisation from ethanol, there are obtained 23.5 g. (89% of theory) N - benzoyl - tyramine, which has a melting point of 165—166°C.

22.5 g. (93 mMol) N - benzoyl - tyramine are introduced into a solution of 2.14 g. (93 mg.-atom) sodium in 50 ml. anhydrous methanol, the alcohol is evaporated off and the residue is freed from residual solvent in a vacuum, using benzene as the entraining agent. The absolutely dry, powdered phenolate is suspended in 100 ml. anhydrous toluene and 26.7 g. (137 mMol) ethyl α - bromoisobutyrate are added thereto. The suspension is maintained for 25 hours at 80°C. and then evaporated in a vacuum. The residue is taken up in methylene chloride, successively washed with dilute aqueous sodium hydroxide solution, hydrochloric acid and water, dried over anhydrous calcium chloride and evaporated. There are obtained 26.1 g. (79% of theory) ethyl α - [4 - benzoylaminoethyl] - phenoxy] - isobutyrate which, after recrystallisation from ether/ligroin (1:10) and again crystallising from acetone, has a melting point of 65—66°C.

In an analogous manner, there are obtained from

a) 4 - chlorobenzoyl chloride and tyramine: di - (4 - chlorobenzoyl) - tyramine

(yield 98%; m.p. 203—205°C.); N - (4 - chlorobenzoyl) - tyramine (yield 91%; m.p. 74—176°C.); and finally ethyl α - [4 - (2 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate (67% of theory; m.p. 96—97°C.);

b) 2 - methoxybenzoyl chloride and tyramine: di - (2 - methoxybenzoyl) - tyramine (yield 95%; m.p. 80—81°C.); N - (2 - methoxybenzoyl) - tyramine (yield 75%; m.p. 166—167°C.); and finally ethyl α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyrate (87% of theory; oil; refractive index 1.4570);

c) 2 - methoxy - 5 - chlorobenzoyl chloride and tyramine: di - (2 - methoxy - 5 - chlorobenzoyl) - tyramine (yield 98%; m.p. 144—145°C.); N - (2 - methoxy - 5 - chlorobenzoyl) - tyramine (yield 93%; m.p. 133—135°C.); and finally ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate (61% of theory; oil; refractive index 1.5460).

Example 2.

α - [4 - (Benzoylaminoethyl) - phenoxy] - isobutyric acid.

35.5 g. (0.1 mol) ethyl α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyrate are suspended in 1.5 litres dioxan and slowly mixed at ambient temperature with 200 ml. 1N aqueous potassium hydroxide solution. The suspension is stirred for two hours at ambient temperature and subsequently for one hour at 40°C., the starting material thereby going fully into solution. Subsequently, the reaction mixture is cooled and neutralised with 200 ml. 1N hydroxychloric acid. Thereafter, the solvent is distilled off in a vacuum and the residue is washed with water until free of salt and recrystallised from acetone. There are obtained 25.5 g. α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyric acid; m.p. 155—156°C.; yield 78% of theory.

In an analogous manner, there are obtained:

a) α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - isobutyric acid

From ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate in a yield of 84% of theory; m.p. 186°C., after recrystallisation from acetone;

b) α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyric acid

From ethyl α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyrate in a yield of 65% of theory; m.p. 131°C., after recrystallisation from acetone; and

c) α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - isobutyric acid

From ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - iso-

butyrate in a yield of 72% of theory; m.p. 137°C. after recrystallisation from acetone.

Example 3.

Ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate

A mixture of 56.8 g. (0.2 mol) N - (4 - chlorobenzoyl) - tyramine, 34.5 g. (0.25 mol) anhydrous potassium carbonate and 500 ml. methyl ethyl ketone is stirred for 2 hours at reflux temperature. Subsequently, 58.5 g. (0.3 mol) ethyl α - bromoisobutyrate are added thereto, and while stirring, the reaction mixture is further boiled for 6 hours. Thereafter, a further 10.5 g. (0.054 mol) ethyl α - bromoisobutyrate and 13.8 g. (0.1 mol) potassium carbonate are added and the reaction mixture maintained at reflux temperature for a further 16 hours. The solid material on the bottom of the reaction vessel used is filtered off and thoroughly washed with hot acetone. The combined filtrates are evaporated in a vacuum and the crystalline residue is recrystallised from acetone. The product is identical with that obtained in Example 1a).

In an analogous manner, there are obtained:

a) ethyl 4 - benzoylaminoethyl - phenoxyacetate

From 4 - benzoylaminoethyl - phenol and ethyl bromoacetate in a yield of 94% of theory. After recrystallisation from ethanol, the product has a melting point of 108—109°C.;

b) ethyl 4 - (4 - chlorobenzoylaminoethyl) - phenoxyacetate

From 4 - (4 - chlorobenzoylaminoethyl) - phenol and ethyl bromoacetate, with a yield of 79% of theory. After recrystallisation from acetone, the product has a melting point of 137°C.;

c) ethyl 4 - (2 - methoxybenzoylaminoethyl) - phenoxyacetate

From 4 - (2 - methoxybenzoylaminoethyl) - phenol and ethyl bromoacetate, with a yield of 80% of theory. After recrystallisation from ether, the product has a melting point of 62—63°C.;

d) ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy acetate

From 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenol and ethyl bromoacetate, with a yield of 70% of theory. After recrystallisation from isopropanol, the product has a melting point of 79—80°C.

Example 4.

4 - Benzoylaminoethyl - phenoxyacetic acid.

4 - Benzoylaminoethyl - phenoxyacetic acid is obtained, in a manner analogous to that described in Example 2, by hydrolysis of the

corresponding ethyl ester (obtained according to Example 3a), using acetone as solvent. The yield is 89% of theory. After recrystallisation from acetone, the product has a melting point of 164—165°C.

In an analogous manner, there are obtained:

- a) 4 - (4 - chlorobenzoylaminoethyl) - phenoxyacetic acid
From ethyl 4 - (4 - chlorobenzoylaminoethyl) - phenoxyacetate in a yield of 83% of theory. After recrystallisation from acetone, the product has a melting point of 199°C.;
- b) 4 - (2 - methoxybenzoylaminoethyl) - phenoxyacetic acid
From ethyl 4 - (2 - methoxybenzoylaminoethyl) - phenoxyacetate in a yield of 72% of theory. After recrystallisation from acetone, the product has a melting point of 146—147°C.; and
- c) 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxyacetic acid
From ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxyacetate in a yield of 89% of theory. After recrystallisation from isopropanol, the product has a melting point of 142—143°C.

Example 5.

- Ethyl α - (4 - benzoylaminoethyl) - phenoxy - isobutyrate
12 g. (75 mMol) 4 - hydroxybenzylamine hydrochloride are dissolved in 100 ml. anhydrous pyridine, 10 g. powdered, anhydrous potassium carbonate are added thereto and 21.1 g. (0.15 mol) benzoyl chloride are added dropwise, the temperature thereby rising spontaneously. Subsequently, the reaction mixture is heated to 90°C., concentrated in a vacuum to one third and stirred into 200 ml. water. The pH is now adjusted to 6.5 with hydrochloric acid and the precipitate formed is filtered off with suction, digested with an aqueous solution of sodium bicarbonate and again acidified. Subsequently, the product is recrystallised from ethanol. There are obtained 22.7 g. (95% of theory) [4 - (benzoylaminoethyl) - phenyl]benzoate, which has a melting point of 141—142°C.

- 16.6 g. (0.05 mol) [4 - (benzoylaminoethyl) - phenyl]benzoate are suspended in 1 litre acetone and saponified with an aqueous solution of potassium hydroxide in the manner described in Example 1. There are obtained 9.85 g. (87% of theory) 4 - benzoylaminoethyl - phenol which, after recrystallisation from ethanol, has a melting point of 155—156°C.

- 4 - Benzoylaminoethyl - phenol is reacted with ethyl α - bromoisobutyrate in a manner analogous to that described in Example 1 to give ethyl α - (4 - benzoylaminoethyl) - phenoxyisobutyrate in a yield of 81% of

theory. After dissolving in ether and reprecipitating with ligroin, the product has a melting point of 75—76°C.

In an analogous manner, there are obtained:

- a) ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate
From 4 - chlorobenzoyl chloride and 4 - hydroxybenzylamine hydrochloride *via* the following intermediate stages: [4 - (4 - chlorobenzoylaminoethyl) - phenyl] 4 - chlorobenzoate (yield 67% of theory; m.p. 174—175°C.); 4 - (4 - chlorobenzoylaminoethyl) - phenol (yield 92% of theory; m.p. 194—195°C.); and finally ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate (yield 74% of theory; m.p. 70—71°C., after dissolving in ether and reprecipitating with ligroin).
- b) ethyl α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyrate
From 2 - methoxybenzoyl chloride and 4 - hydroxybenzylamine hydrochloride *via* the following intermediate stages: [4 - methoxybenzoylaminoethyl) - phenyl] 2 - methoxybenzoate (yield 74% of theory; m.p. 113—114°C.); 4 - (2 - methoxybenzoylaminoethyl) - phenol (yield 72% of theory; m.p. 146—147°C.); and finally ethyl α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyrate (yield 63% of theory, non-distillable oil; n_D^{20} : 1.5535).
- c) ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate
From 2 - methoxy - 5 - chlorobenzoyl chloride and 4 - hydroxybenzylamine hydrochloride *via* the following intermediate stages: [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenyl] 2 - methoxy - 4 - chlorobenzoate (yield 54% of theory; m.p. 145—146°C.); 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenol (yield 90% of theory; m.p. 159—160°C.); and finally ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate (yield 82% of theory; m.p. 82—83°C.).

Example 6.

Ethyl 4 - benzoylaminoethyl - phenoxyacetate.

A mixture of 20.0 g. 4 - benzoylaminoethyl - phenol, 12.2 g. (88 mMol) powdered potassium carbonate and 200 ml. anhydrous methyl ethyl ketone are maintained at reflux temperature, while stirring, then cooled somewhat and 16.8 g. (0.1 mol) ethyl bromoacetate and some potassium iodide added thereto and further maintained at reflux temperature for 6 hours. The inorganic components are filtered off with suction and washed with chloroform. The filtrates are com-

- bined, extracted with diluent aqueous sodium hydroxide solution, washed neutral with water and dried over anhydrous calcium chloride. After evaporation in a vacuum, the residue obtained is recrystallised from acetone. There is obtained ethyl 4 - benzoylaminoethyl-phenoxycetate in a yield of 77% of theory; m.p. 96—97°C.
 In an analogous manner, there are obtained:
- 10 a) -ethyl 4 - (4 - chlorobenzoylaminoethyl) - phenoxycetate
 From 4 - (4 - chlorobenzoylaminoethyl) - phenol and ethyl bromoacetate in a yield of 68% of theory. After recrystallisation from acetone, the product has a melting point of 125—126°C.;
- 15 b) ethyl 4 - (2 - methoxybenzoylaminoethyl) - phenoxycetate
 From 4 - (2 - methoxybenzoylaminoethyl) - phenol and ethyl bromoacetate in a yield of 70% of theory. The product is an oil with a refractive index of 1.5685;
- 20 c) ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxycetate
 From 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenol and ethyl bromoacetate in a yield of 78% of theory. After recrystallisation from isopropanol, the product has a melting point of 86—87°C.
- 25 d) ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxycetate
 From 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenol and ethyl bromoacetate in a yield of 78% of theory. After recrystallisation from isopropanol, the product has a melting point of 86—87°C.
- 30 **Example 7.**
 The following products are obtained in a manner analogous to that described in Example 2:
- 35 a) α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyric acid
 From ethyl α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyrate in a yield of 52% of theory; after recrystallisation from ethanol, the product has a melting point of 168—169°C.;
- 40 b) α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - isobutyric acid
 From ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy]isobutyrate in a yield of 87% of theory; after recrystallisation from ethanol, the product has a melting point of 191—192°C.;
- 45 c) α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyric acid
 From ethyl α - [4 - (2 - methoxybenzoylaminoethyl) - phenoxy] - isobutyrate in a yield of 89% of theory; after recrystallisation from acetone, the product has a melting point of 114°C.;
- 50 d) α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - isobutyric acid
 From ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxy] - isobutyrate in a yield of 72% of theory; after recrystallisation from acetone, the product has a melting point of 146—147°C.;
- 55 e) 4 - benzoylaminoethyl - phenoxycetic acid
 From ethyl 4 - benzoylaminoethyl - phenoxycetate in a yield of 90% of theory; after recrystallisation from acetone, the product has a melting point of 153—154°C.;
- 60 f) 4 - (4 - chlorobenzoylaminoethyl) - phenoxycetic acid
 From ethyl 4 - (4 - chlorobenzoylaminoethyl) - phenoxycetate in a yield of 73% of theory; after recrystallisation from acetone, the product has a melting point of 170—171°C.;
- 65 g) 4 - (2 - methoxybenzoylaminoethyl) - phenoxycetic acid
 From ethyl 4 - (2 - methoxybenzoylaminoethyl) - phenoxycetate in a yield of 73% of theory; after recrystallisation from acetone, the product has a melting point of 158—159°C.;
- 70 h) 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxycetic acid
 From ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminoethyl) - phenoxycetate in a yield of 88% of theory; after recrystallisation from ethanol, the product has a melting point of 152—153°C.
- 75 **Example 8.**
 Ethyl α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyrate.
- 80 A mixture of 44.8 g. (0.25 mol) N - acetyl - tyramine, 69.5 g. (0.5 mol) anhydrous, powdered potassium carbonate and 750 ml. anhydrous butan - 2 - one are heated under reflux for 2 hours, while stirring, 73.2 g. (0.375 mol) ethyl α - bromoisobutyrate and 1 g. potassium iodide then added thereto and the reaction mixture further heated under reflux.
- 85 After boiling for 40 and 70 hours respectively, there are, in each case, added a further 35 g. potassium carbonate and 36.6 g. ethyl α -bromoisobutyrate. After a total reaction period of 130 hours, the reaction mixture is evaporated in a vacuum, poured into ice water and then extracted with ether. The ethereal extract is washed three times with 0.5N aqueous sodium hydroxide solution, then with water and finally dried over anhydrous calcium chloride and evaporated. There remain 83.8 g. of an oily residue, which still contains ethyl α -bromoisobutyrate. The oil is maintained for 5 hours at 70°C. and at a pressure of 0.1 mm.Hg., then cooled. The resultant crystalline slurry is washed with ligroin and dried. There are obtained 69.8 g. (95% of theory) of product. The melting point of the still not quite
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pure ethyl α - [4 - (2 - acetaminoethyl) - phenoxy] - isobutyrate is 48—51°C.

A solution of 119.1 g. (0.407 mol) ethyl α - [4 - (2 - acetaminoethyl) - phenoxy] - isobutyrate in 750 ml. alcohol is mixed with a solution of 224.4 g. (4.00 mol) potassium hydroxide in 800 ml. water and heated under reflux for 8 hours. While cooling, there are added exactly 4.00 ml. hydrogen chloride (for example, in the form of 2N hydrochloric acid), the reaction mixture then further cooled and, after some time, the crystals which separate out are filtered off with suction. These are washed with water and dried; there are obtained 48.4 g. (53% of theory) of product which melts, with decomposition, at 274°C. From the mother liquor there are obtained, after distilling off the alcohol and cooling, a further 32.5 g. (36% of theory) of product, with a melting point of 263—270°C. The crude α - [4 - (2 - aminoethyl) - phenoxy] - isobutyric acid thus obtained is recrystallised from alcohol-water (4:1 by volume) and then has a melting point of 284°C. The corresponding hydrochloride has a melting point of 187—189°C.

A solution of 58 g. (0.26 mol) of this carboxylic acid in 600 ml. absolute alcohol is gasified, while stirring and with ice cooling, from the surface with dry hydrogen chloride until the solution is saturated. The reaction mixture is left to stand for 12 hours in a closed vessel. Subsequently, the alcohol and hydrogen chloride are removed in a vacuum. The residue is then poured into water and extracted three times with ether and the aqueous phase is rendered clearly alkaline and extracted three times with chloroform. The combined chloroform extracts are washed with a little water, dried over anhydrous potassium carbonate and then evaporated. By distillation of the residue, there are obtained, between 125 and 128°C./0.1 mm.Hg., 53.2 g. (82% of theory) colourless ethyl α - [4 - (2 - aminoethyl) - phenoxy] - isobutyrate.

By the reaction of 1 mol ethyl α - [4 - (2 - aminoethyl) - phenoxy] - isobutyrate with 1 mol benzoyl chloride in a manner analogous to that described in Example 1, there is obtained, in a yield of 97% of theory, ethyl α - [4 - (benzoylaminoethyl) - phenoxy] - isobutyrate, which has a melting point of 65—66°C. The mixed melting point with the compound prepared according to Example 1 shows no depression.

For the preparation of the N - acetyl - tyramine used as starting material, there can be used, for example, one of the two following methods:

1. 64.0 g. (0.466 mol) tyramine are mixed, while stirring, with 200 ml. acetic anhydride, the mixture undergoing spontaneous heating up and a clear solution being formed. This solution is seeded with a few crystals of N -

acetyl - tyramine, crystallisation taking place immediately. The reaction mixture is cooled rapidly, filtered with suction, washed with ether and water and dried. There are obtained 59 g. (71% of theory) N - acetyl - tyramine, which has a melting point of 124—126°C. By evaporation of the mother liquor, dissolving of the residue in a dilute aqueous solution of sodium hydroxide, filtration and acidification of the filtrate, there are obtained a further 5.5 g. (6% of theory) of product with a melting point of 122—124°C. After recrystallisation from ethyl acetate, and N - acetyl - tyramine melts at 129—131°C.

2. 65.8 g. (0.84 mol) acetyl chloride are added dropwise, with stirring, at 30—35°C. to a solution of 54.9 g. (0.4 mol) tyramine in 200 ml. pyridine. Subsequently, the reaction mixture is heated for 15 minutes on a boiling waterbath, then cooled and poured into an ice-water mixture. It is then rendered clearly acidic by the addition of concentrated hydrochloric acid and subsequently extracted with chloroform. The chloroform phase is washed with water, dried over anhydrous calcium chloride and then evaporated. There remains a residue of 88.5 g. (quantitative yield) diacetyl-tyramine which, after recrystallisation from benzene, has a melting point of 99—100°C. The diacetyl-tyramine is now dissolved in 500 ml. methanol. 800 ml. (0.8 mol) 1N potassium hydroxide solution are now added dropwise, the temperature thereby increasing to about 30°C., and the reaction mixture maintained at an internal temperature of 50°C. for 2 hours. It is then cooled, rendered weakly acidic with concentrated hydrochloric acid and the methanol evaporated off in a vacuum. The product which crystallises out is filtered off with suction, thoroughly washed with water and then dried. There are obtained 58.3 g. (81% of theory) N - acetyl - tyramine which, after recrystallisation from ethyl acetate, has a melting point of 131°C.

Example 9.

Ethyl 4-benzoylaminoethyl-phenoxyacetate
In a manner analogous to that described in Example 3, from 4 - (acetaminomethyl) - phenol and ethyl bromoacetate there is obtained ethyl 4 - (acetaminomethyl) - phenoxyacetate in a yield of 92% of theory. After recrystallisation from isopropanol, it has a melting point of 90—91°C.

By saponification of ethyl 4 - (acetaminomethyl) - phenoxyacetate in the manner described in Example 8, there is obtained 4 - (aminomethyl) - phenoxyacetic acid in a yield of about 90% of theory; m.p. 231—232°C.

From this carboxylic acid there is obtained, by esterification with ethanol and hydrogen chloride in a manner analogous to that described in Example 8, ethyl 4 - (aminomethyl) - phenoxyacetate, the yield being 71% of theory. After recrystallisation from ethanol, the cor-

responding hydrochloride has a melting point of 190—191°C.

This compound is benzoylated in a manner analogous to that described in Example 5 to give ethyl 5 - benzoylaminoethyl - phenoxyacetate in a yield of 90% of theory; m.p. 96—97°C. The mixed melting point with the compound prepared according to Example 6 shows no depression.

The 4 - (acetaminomethyl) - phenol used as starting material is prepared in the following manner: 14.9 ml. (0.2 mol) acetyl chloride is added dropwise, with cooling, to a solution of 15.9 g. (0.1 mol) 4 - hydroxybenzylamine in 100 ml. anhydrous pyridine. The reaction mixture is subsequently stirred for one hour at 20°C., then heated in a boiling waterbath for 15 minutes and acidified with concentrated hydrochloric acid. The acidic solution is extracted with chloroform and the chloroform phase is dried over anhydrous sodium sulphate and then evaporated. The crude 4 - (acetaminomethyl) - phenyl acetate is dissolved in ethyl acetate and again precipitated out by the addition of ligroin. There is obtained a yield of 18.86 g. (91% of theory); m.p. 78—79°C.

By heating for 2 hours a mixture of 4 - (acetaminomethyl) - phenyl acetate, methanol and 1N aqueous potassium hydroxide solution, there is obtained, in a manner analogous to that described in Example 1, paragraph 2, 84% of theory 4 - (acetaminomethyl) - phenol which, after recrystallisation from isopropanol, has a melting point of 131—132°C.

In an analogous manner, ethyl α - (4 - benzoylaminoethyl) - phenoxy - isobutyrate is obtained from 4 - (acetaminomethyl) - phenol and ethyl α - bromoisobutyrate via the following intermediate stages: ethyl α - [4 - (acetaminomethyl) - phenoxy] - isobutyrate (yield 90% of theory; m.p. 84—85°C. after recrystallisation from ether/ligroin); α - [4 - (acetaminomethyl) - phenoxy] - isobutyric acid [by heating for 5 hours at 60°C. a mixture of 108 g. (0.39 mol) ethyl α - [4 - (acetaminomethyl) - phenoxy] - isobutyrate, 1.5 litres methanol and 635 ml. 1N aqueous potassium hydroxide solution and subsequent neutralisation with 635 ml. 1N hydrochloric acid, then evaporation in a vacuum; m.p. 155—157°C., after recrystallisation from isopropanol]; α - [4 - (aminomethyl) - phenoxy] - isobutyric acid (yield 84% of theory; m.p. 221—222°C.); ethyl α - [4 - (aminomethyl) - phenoxy] - isobutyrate (yield 49% of theory; b.p. 113—120°C./0.06 mm.Hg.); the compound obtained in 95% yield by subsequent benzoylation melts at 75—76°C. and shows no melting point depression in admixture with compound obtained according to Example 5.

Example 10.

α {4 - [3 - (4 - chlorobenzoylamino) - propyl] - phenoxy} - isobutyric acid 65
26.2 g. (0.15 mol) 4 - chlorobenzoyl chloride are added dropwise to a solution of 37.0 g. (0.133 mol) 3 - (4 - benzyloxyphenyl) - propylamine hydrochloride in 500 ml. pyridine. Subsequently, the reaction mixture is maintained for 15 minutes on a boiling waterbath, then cooled and poured into 2 litres water. The product which precipitates is filtered off with suction, digested with an aqueous solution of sodium bicarbonate, washed with water, dried and recrystallised from ethanol. There are obtained 41.5 g. (82% of theory) 4 - chlorobenzoic acid [3 - (4 - benzyloxyphenyl) - propylamine] in the form of yellowish crystals; m.p. 128—129°C. 70

A mixture of 45.5 g. (0.12 mol) 4 - chlorobenzoic acid [3 - (4 - benzyloxyphenyl) - propylamide], 600 ml. dimethyl formamide and 2 g. palladium charcoal (10% Pd) is gasified at atmospheric pressure with the calculated amount of hydrogen. Subsequently, the catalyst is filtered off and the filtrate evaporated in a vacuum. The crystalline evaporation residue can be recrystallised from isopropanol. There are obtained 24.7 g. (72% of theory) 4 - chlorobenzoic acid [3 - (4 - hydroxyphenyl) - propylamide]; m.p. 146—147°C. 85

A mixture of 14.5 g. (50 mMol) 4 - chlorobenzoic acid [3 - (4 - hydroxyphenyl) - propylamide], 6.9 g. (50 mMol) powdered, dry potassium carbonate and 200 ml. anhydrous butan - 2 - one is stirred for 2 hours at 80°C., and then 9.8 g. (50 mMol) ethyl α - bromoisobutyrate, as well as 0.5 g. potassium iodide, are added and the reaction mixture maintained at reflux temperature for 24 hours. After the addition of a further 3.45 g. potassium carbonate and 4.9 g. ethyl α - bromoisobutyrate, the reaction mixture is heated under reflux for 72 hours, subsequently evaporated in a vacuum and the contents of the reaction flask used taken up in chloroform. The chloroform phase is extracted with dilute aqueous sodium hydroxide solution, washed neutral with water, finally dried over anhydrous calcium chloride and evaporated. There remain behind 8.5 g. of an oily substance which consists of almost pure ethyl α - {4 - [3 - (4 - chlorobenzoylamino) - propyl] - phenoxy} - isobutyrate. 100

4.0 g. (10 mMol) of this ethyl ester are dissolved in 50 ml. methanol and stirred with 15 ml. (15 mMol) 1N aqueous potassium hydroxide solution for 1 hour at 40—50°C. Subsequently, the reaction mixture is neutralised with 15 ml. 1N hydrochloric acid, the methanol is distilled off in a vacuum, the 115 120

precipitate formed is filtered off with suction and the aqueous phase is extracted with ether. After evaporation of the ether, there remains a semi-solid residue which is combined with the precipitate and recrystallised from isopropanol. There are obtained 2.5 g. (68% of theory) α - {4 - [3 - (4 - chlorobenzoylamino) - propyl] - phenoxy} - isobutyric acid; m.p. 121—122°C.

For the preparation of the 3 - (4 - benzyloxyphenyl) - propylamine used as starting material, the following method is used: a solution of 45 g. (0.271 mol) 3 - (4 - hydroxyphenyl) - propionic acid in 250 ml. dimethyl sulphoxide is mixed with 70 g. powdered, dry potassium carbonate and stirred for 1 hour at 80—85°C. and then cooled. Subsequently, 75.5 g. (0.596 mol) benzoyl chloride are added thereto dropwise and the reaction mixture stirred for 2 hours at 80—85°C. After suction filtration, the filtrate is evaporated under oil pump vacuum and the oily residue cooled, whereby it crystallises. After recrystallisation thereof from ethanol, there are obtained 74.0 g. (79% of theory) colourless benzoyl 3 - (4 - benzyloxyphenyl) - propionate; m.p. 43—44°C.

59 g. (0.155 mol) of this benzyl ester are stirred for 7 hours at 20°C with 325 ml. 2N aqueous potassium hydroxide solution and 210 ml. ethanol. Subsequently, the solution is adjusted to pH 6.5 with hydrochloric acid and the alcohol distilled off. A part of the acid thereby already precipitates out. Water is added to the distillation residue, which is then rendered strongly acidic with hydrochloric acid and filtered. The filter cake obtained is washed with water, dried and finally recrystallised from ethanol. There are obtained 34 g. (92% of theory) colourless 3 - (4 - benzyloxyphenyl) - propionic acid; m.p. 121—122°C.

A mixture of 128 g. (0.5 mol) 3 - (4 - benzyloxyphenyl) - propionic acid, 69 ml. triethylamine and 500 ml. anhydrous chloroform are added dropwise, with stirring, at -30°C. to a solution of 46 ml. ethyl chloroformate in 500 ml. anhydrous chloroform. Subsequently, the reaction mixture is stirred for 1.5 hours, without external cooling, the internal temperature thereby increasing to -5°C. At this temperature of -5°C., a slow current of dry gaseous ammonia is passed in, while stirring. The reaction mixture is left to stand overnight in a closed vessel, filtered with suction, shaken out with cold 0.5N aqueous sodium hydroxide solution, thereafter washed with water and the chloroform phase dried over anhydrous sodium sulphate. After evaporation in a vacuum, the evaporation residue is recrystallised from alcohol. In this manner, there is obtained 3 - (4 - benzyloxyphenyl) - propionamide in a yield of 80% of theory; m.p. 159—160°C.

Into a round-bottom flask, equipped with a

Soxhlet extractor, the thimble of which contains 12.8 g. (50 mMol) 3 - (4 - benzyloxyphenyl) - propionamide, there is placed a mixture of 7.6 g. (0.2 mol) lithium aluminium hydride and 100 ml. anhydrous tetrahydrofuran, followed by heating for 20 hours at reflux temperature, whereby the amide is slowly extracted from the thimble and passed to the reducing agent. Subsequently, decomposition is carried out by the addition of 8 ml. water, 8 ml. 15% aqueous sodium hydroxide solution and again with 24 ml. water, in the given order, while cooling. The precipitate formed is filtered off with suction and washed with tetrahydrofuran. After evaporation of the tetrahydrofuran, 12.2 g. of a viscous yellow oil remain behind, which is dissolved in 40 ml. dioxan. After filtration, the filtrate is mixed with hydrogen chloride-containing dioxan, the precipitated hydrochloride is filtered off with suction and recrystallised from dioxan to which a small amount of concentrated hydrochloric acid had been added. There are obtained 10.2 g. (73% of theory) 3 - (4 - benzyloxyphenyl) - propylamine hydrochloride; m.p. 230—233°C.

Example 11.

In a manner analogous to that described in Example 3, there is obtained ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - propionate from 4 - (4 - chlorobenzoylaminoethyl) - phenol and ethyl α - bromopropionate, the yield being 77% of theory. After recrystallisation from alcohol, the product has a melting point of 127°C.

Example 12.

In a manner analogous to that described in Example 4, there is obtained α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - propionic acid from ethyl α - [4 - (4 - chlorobenzoylaminoethyl) - phenoxy] - propionate, the yield being 90% of theory. After recrystallisation from ethanol, the product has a melting point of 185—186°C.

Example 13.

Ethyl α - [4 - (2 - methylbenzoylaminoethyl) - phenoxy] - isobutyrate 45.15 g. (292 mMol) 2 - methylbenzoyl chloride are added dropwise, within the course of 10 minutes, to 20.1 g. (146 mMol) tyramine in 60 ml. anhydrous pyridine, while stirring and with the exclusion of moisture and thereafter rinsed with 50 ml. anhydrous pyridine. The solution, which automatically heats up during the addition of the 2 - methylbenzoyl chloride, is subsequently heated to 100°C. for 15 minutes in order to complete the reaction, then cooled to 35°C. and poured into a mixture of about 500 g. ice and water. The resultant crystalline slurry is acidified with dilute hydrochloric acid, filtered off with suction, washed with dilute hydrochloric acid,

water and aqueous sodium bicarbonate solution and dried. After recrystallisation from acetone, there are obtained 49.2 g. (90% of theory) di - (2 - methylbenzoyl) - tyramine which, after further recrystallisation from ethanol, has a melting point of 129—130°C.

41.0 g. (0.11 mol) di - (2 - methylbenzoyl) - tyramine are suspended in 400 ml. methanol, 130 ml. 2N aqueous potassium hydroxide solution are added thereto and the mixture heated to 50—45°C. for 1 hour. After cooling, 130 ml. 2N hydrochloric acid are added. The precipitate formed is filtered off with suction, the filtrate freed from methanol in a vacuum and the precipitate thereby obtained combined with the hydrochloric acid precipitate. The combined precipitates are washed with water and, for the removal of any benzoic acid which may be present, are digested with an aqueous solution of sodium bicarbonate. After recrystallisation from ethanol, there are obtained 20.8 g. (74% of theory) N - (2 - methylbenzoyl) - tyramine, which has a melting point of 108—109°C.

This compound can advantageously also be prepared according to the following one-spot process:

13.7 g. (0.1 mol) tyramine are stirred into a solution of 23 g. (0.41 mol) potassium hydroxide in 300 ml. water, 32.4 g. (0.21 mol) 2-methylbenzoyl chloride then added thereto dropwise, a precipitate thereby forming immediately, whereafter the reaction mixture is stirred for 1 hour. Subsequently, 600 ml. methanol are added and the reaction mixture maintained at a temperature between 40 and 50°C. for 2 hours, while further stirring. The methanol is then evaporated off in a vacuum and the residue weakly acidified with hydrochloric acid. The precipitate formed is filtered off with suction, then digested with an aqueous solution of sodium bicarbonate and again filtered off with suction. After drying, the product is recrystallised from ethanol and then from acetone. There is obtained N - (2 - methylbenzoyl) - tyramine in an amount of 22.5 g. (88% of theory); m.p. 108—109°C.

A mixture of 51.5 g. (0.2 mol) N - (2 - methylbenzoyl) - tyramine, 34.5 g. (0.25 mol) dry potassium carbonate and 500 ml. methyl ethyl ketone is maintained at reflux temperature for 2 hours, while stirring. Subsequently, 58.5 g. (0.3 mol) ethyl α - bromoisobutyrate are added thereto and the reaction mixture boiled for a further 6 hours, while stirring. Thereafter, a further 10.5 g. (0.054 mol) ethyl α - bromoisobutyrate and 13.8 g. (0.1 mol) potassium carbonate are added thereto and the reaction mixture further refluxed for 16 hours. The solid material on the bottom of the reaction vessel used is filtered off and thoroughly washed with acetone. The combined filtrates are evaporated in a vacuum and the crystalline residue is recrystallised

from acetone. In this manner, there is obtained ethyl α - [4 - (2 - methylbenzoylaminoethyl) - phenoxy] - isobutyrate in a yield of 62% of theory. After recrystallisation from ethanol, the product has a melting point of 82°C.

In an analogous manner, from 4 - methylbenzoyl chloride and tyramine, there is obtained: di - (4 - methylbenzoyl) - tyramine (yield 77%; m.p. 186°C.); N - (4 - methylbenzoyl) - tyramine (yield 90%; m.p. 178°C.); and finally ethyl α - [4 - (4 - methylbenzoylaminoethyl) - phenoxy] - isobutyrate (yield 75%; m.p. 99°C.).

Example 14.

α - [4 - (2 - Methylbenzoylaminoethyl) - phenoxy] - isobutyric acid

36.95 g. (0.1 mol) ethyl α - [4 - (2 - methylbenzoylaminoethyl) - phenoxy] - isobutyrate are suspended in 400 ml. methanol and mixed at ambient temperature with 200 ml. 1N aqueous potassium hydroxide solution. The suspension is stirred for 2 hours at 40—50°C., whereby the starting material goes completely into solution, cooled and neutralised with 200 ml. 1N hydrochloric acid. Thereafter, the solvent is distilled off in a vacuum and the residue is washed free of salt and recrystallised from acetone. There are obtained 30.2 g. α - [2 - (2 - methylbenzoylaminoethyl) - phenoxy] - isobutyric acid (89% of theory); m.p. 144—145°C.

In an analogous manner, there is obtained α - [4 - (4 - methylbenzoylaminoethyl) - phenoxy] - isobutyric acid; yield 93%; m.p. 170—171°C.

Example 15.

Ethyl α - [4 - (2 - methylbenzoylamino-methyl) - phenoxy] - isobutyrate

12 g. (75 mMol) 4 - hydroxybenzylamine hydrochloride are dissolved in 100 ml. anhydrous pyridine, 10 g. powdered anhydrous potassium carbonate are added thereto and 23.2 g. (0.15 mol) 2 - methylbenzoyl chloride added dropwise, the temperature thereby increasing spontaneously. Subsequently, the reaction mixture is heated for 80 minutes to 90°C., concentrated in a vacuum to one third, cooled and stirred into 200 ml. water. The mixture is now adjusted to pH 6.5 with hydrochloric acid and the precipitate formed is filtered off with suction and thereafter recrystallised from ethanol. There are obtained 25.0 g. (93% of theory) [4 - (2 - methylbenzoylaminoethyl) - phenyl] 2 - methylbenzoate, which has a melting point of 134—135°C.

18.0 g. (0.05 mol) [4 - (2 - methylbenzoylaminoethyl) - phenyl] 2 - methylbenzoate are suspended in a litre acetone and saponified with aqueous potassium hydroxide solution in the manner described in Example 1. There are obtained 9.85 g. (81% of theory) 4 - (2 -

methylbenzoylaminomethyl) - phenol which, after recrystallisation from ethanol, has a melting point of 161—162°C.

- 4 - (2 - Methylbenzoylaminomethyl) - phenol is reacted with ethyl α - bromoisobutyrate in a manner analogous to that described in Example 1 to give ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate, the yield being 80% of theory.
- 10 After reprecipitation from ether/ligroin, the product has a melting point of 74—75°C.

- In an analogous manner, α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyric acid ethyl ester is obtained from 4 - methylbenzoyl chloride and 4 - hydroxybenzylamine hydrochloride *via* the following intermediate stages: [4 - (4 - methylbenzoylaminomethyl) - phenyl] 4 - methylbenzoate (yield 80% of theory; m.p. 186°C.); 4 - (4 - methylbenzoylaminomethyl) - phenol (yield 81% of theory; m.p. 136—137°C.); and finally ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate (yield 78% of theory; m.p. 80—81°C., after recrystallisation from ether/ligroin).

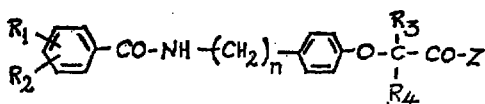
Example 16.

The following compounds are obtained in a manner analogous to that described in Example 2:

- 30 a) α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyric acid
- From ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate in a yield of 78% of theory. After recrystallisation from acetone, the compound melts at 127—128°C.;
- 35 b) α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyric acid
- From ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate in a yield of 84% of theory. After recrystallisation from acetone, the compound melts at 163—165°C.

WHAT WE CLAIM IS:—

- 45 1. Compounds of the general formula:—



- wherein R_1 and R_2 , which may be the same or different, are hydrogen or halogen atoms or alkyl or alkoxy radicals containing up to 5 carbon atoms, R_3 and R_4 , which may be the same or different, the hydrogen atoms or alkyl radicals containing up to 5 carbon atoms, n is 1, 2 or 3 and Z is a hydroxyl group or an alkoxy radical containing up to 5 carbon atoms; and the pharmacologically compatible salts thereof.

2. Ethyl α - [4 - (benzoylaminomethyl) - phenoxy] - isobutyrate.
3. Ethyl α - [4 - (4 - chlorobenzoylaminomethyl) - phenoxy] - isobutyrate. 60
4. Ethyl α - [4 - (2 - methoxybenzoylaminomethyl) - phenoxy] - isobutyrate.
5. Ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminomethyl) - phenoxy] - isobutyrate.
6. α - [4 - Benzoylaminomethyl) - phenoxy] - isobutyric acid. 65
7. α - [4 - (4 - Chlorobenzoylaminomethyl) - phenoxy] - isobutyric acid.
8. α - [4 - 2 - Methoxybenzoylaminomethyl) - phenoxy] - isobutyric acid. 70
9. α - [4 - (2 - Methoxy - 5 - chlorobenzoylaminomethyl) - phenoxy] - isobutyric acid.
10. Ethyl 4 - benzoylaminomethyl - phenoxyacetate. 75
11. Ethyl 4 - (4 - chlorobenzoylaminomethyl) - phenoxyacetate.
12. Ethyl 4 - (2 - methoxybenzoylaminomethyl) - phenoxyacetate.
13. Ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminomethyl) - phenoxyacetate. 80
14. 4 - Benzoylaminomethyl - phenoxyacetic acid.
15. 4 - (4 - Chlorobenzoylaminomethyl) - phenoxyacetic acid. 85
16. 4 - (2 - Methoxybenzoylaminomethyl) - phenoxyacetic acid.
17. 4 - (2 - Methoxy - 5 - chlorobenzoylaminomethyl) - phenoxyacetic acid.
18. α - [4 - [3 - (4 - Chlorobenzoylaminomethyl) - propyl] - phenoxy] - isobutyric acid. 90
19. Ethyl α - [4 - [3 - (4 - chlorobenzoylaminomethyl) - propyl] - phenoxy] - isobutyrate.
20. Ethyl α - [4 - (4 - chlorobenzoylaminomethyl) - phenoxy] - propionate. 95
21. α - [4 - (4 - Chlorobenzoylaminomethyl) - phenoxy] - propionic acid.
22. Ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate.
23. Ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate. 100
24. α - [4 - (2 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid.
25. α - [4 - (4 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid. 105
26. Ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate.
27. Ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate.
28. α - [4 - (2 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid. 110
29. α - [4 - (4 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid.
30. Ethyl α - [4 - benzoylaminomethyl) - phenoxy] - isobutyrate. 115
31. Ethyl α - [4 - (4 - chlorobenzoylaminomethyl) - phenoxy] - isobutyrate.
32. Ethyl α - [4 - (2 - methoxybenzoylaminomethyl) - phenoxy] - isobutyrate.
33. Ethyl α - [4 - (2 - methoxy - 5 - 120

methylbenzoylaminomethyl) - phenol which, after recrystallisation from ethanol, has a melting point of 161—162°C.

- 4 - (2 - Methylbenzoylaminomethyl) - phenol is reacted with ethyl α - bromoisobutyrate in a manner analogous to that described in Example 1 to give ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate, the yield being 80% of theory.
- 10 After reprecipitation from ether/ligroin, the product has a melting point of 74—75°C.

- In an analogous manner, α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyric acid ethyl ester is obtained from 4 - methylbenzoyl chloride and 4 - hydroxybenzylamine hydrochloride *via* the following intermediate stages: [4 - (4 - methylbenzoylaminomethyl) - phenyl] 4 - methylbenzoate (yield 80% of theory; m.p. 186°C.); 4 - (4 - methylbenzoylaminomethyl) - phenol (yield 81% of theory; m.p. 136—137°C.); and finally ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate (yield 78% of theory; m.p. 80—81°C., after recrystallisation from ether/ligroin).

Example 16.

The following compounds are obtained in a manner analogous to that described in Example 2:

- 30 a) α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyric acid

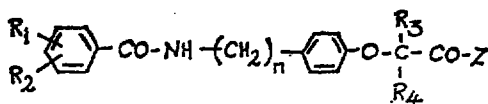
- From ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate in a yield of 78% of theory. After recrystallisation from acetone, the compound melts at 127—128°C.;

- b) α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyric acid

- 40 From ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate in a yield of 84% of theory. After recrystallisation from acetone, the compound melts at 163—165°C.

WHAT WE CLAIM IS:—

- 45 1. Compounds of the general formula:—



- wherein R_1 and R_2 , which may be the same or different, are hydrogen or halogen atoms or alkyl or alkoxy radicals containing up to 5 carbon atoms, R_3 and R_4 , which may be the same or different, the hydrogen atoms or alkyl radicals containing up to 5 carbon atoms, n is 1, 2 or 3 and Z is a hydroxyl group or an alkoxy radical containing up to 5 carbon atoms; and the pharmacologically compatible salts thereof.

2. Ethyl α - [4 - (benzoylaminomethyl) - phenoxy] - isobutyrate.

3. Ethyl α - [4 - (4 - chlorobenzoylaminomethyl) - phenoxy] - isobutyrate. 60

4. Ethyl α - [4 - (2 - methoxybenzoylaminomethyl) - phenoxy] - isobutyrate.

5. Ethyl α - [4 - (2 - methoxy - 5 - chlorobenzoylaminomethyl) - phenoxy] - isobutyrate.

6. α - [4 - Benzoylaminomethyl) - phenoxy] - isobutyric acid. 65

7. α - [4 - (4 - Chlorobenzoylaminomethyl) - phenoxy] - isobutyric acid.

8. α - [4 - 2 - Methoxybenzoylaminomethyl) - phenoxy] - isobutyric acid. 70

9. α - [4 - (2 - Methoxy - 5 - chlorobenzoylaminomethyl) - phenoxy] - isobutyric acid.

10. Ethyl 4 - benzoylaminomethyl - phenoxyacetate. 75

11. Ethyl 4 - (4 - chlorobenzoylaminomethyl) - phenoxyacetate.

12. Ethyl 4 - (2 - methoxybenzoylaminomethyl) - phenoxyacetate.

13. Ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminomethyl) - phenoxyacetate. 80

14. 4 - Benzoylaminomethyl - phenoxyacetic acid.

15. 4 - (4 - Chlorobenzoylaminomethyl) - phenoxyacetic acid. 85

16. 4 - (2 - Methoxybenzoylaminomethyl) - phenoxyacetic acid.

17. 4 - (2 - Methoxy - 5 - chlorobenzoylaminomethyl) - phenoxyacetic acid.

18. α - {4 - [3 - (4 - Chlorobenzoylaminomethyl) - propyl] - phenoxy} - isobutyric acid. 90

19. Ethyl α - {4 - [3 - (4 - chlorobenzoylaminomethyl) - propyl] - phenoxy} - isobutyrate.

20. Ethyl α - [4 - (4 - chlorobenzoylaminomethyl) - phenoxy] - propionate. 95

21. α - [4 - (4 - Chlorobenzoylaminomethyl) - phenoxy] - propionic acid.

22. Ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate.

23. Ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate. 100

24. α - [4 - (2 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid.

25. α - [4 - (4 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid. 105

26. Ethyl α - [4 - (2 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate.

27. Ethyl α - [4 - (4 - methylbenzoylaminomethyl) - phenoxy] - isobutyrate.

28. α - [4 - (2 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid. 110

29. α - [4 - (4 - Methylbenzoylaminomethyl) - phenoxy] - isobutyric acid.

30. Ethyl α - [4 - benzoylaminomethyl) - phenoxy] - isobutyrate. 115

31. Ethyl α - [4 - (4 - chlorobenzoylaminomethyl) - phenoxy] - isobutyrate.

32. Ethyl α - [4 - (2 - methoxybenzoylaminomethyl) - phenoxy] - isobutyrate.

33. Ethyl α - [4 - (2 - methoxy - 5 - 120



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chlorobenzoylaminomethyl) - phenoxy] - isobutyrate.

34. Ethyl 4 - benzoylaminomethyl - phenoxyacetate.

5 35. Ethyl 4 - (4 - chlorobenzoylamine-methyl) - phenoxyacetate.

36. Ethyl 4 - (2 - methoxybenzoylaminomethyl) - phenoxyacetate.

10 37. Ethyl 4 - (2 - methoxy - 5 - chlorobenzoylaminomethyl) - phenoxyacetate.

38. α - [4 - (Benzoylaminomethyl) - phenoxy] - isobutyric acid.

39. α - [4 - (4 - Chlorobenzoylaminomethyl) - phenoxy] - isobutyric acid.

15 40. α - [4 - (2 - Methoxybenzoylaminomethyl) - phenoxy] - isobutyric acid.

41. α - [4 - (2 - Methoxy - 5 - chlorobenzoylaminomethyl) - phenoxy] - isobutyric acid.

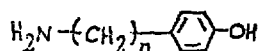
20 42. 4 - Benzoylaminomethyl - phenoxyacetic acid.

43. 4 - (4 - Chlorobenzoylaminomethyl) - phenoxyacetic acid.

25 44. 4 - (2 - Methoxybenzoylaminomethyl) - phenoxyacetic acid.

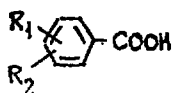
45. 4 - (2 - Methoxy - 5 - chlorobenzoylaminomethyl) - phenoxyacetic acid.

30 46. Process for the preparation of compounds of the general formula given in claim 1, wherein an amine of the general formula:—

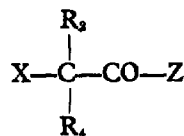


in which n has the same meaning as in claim 1, is reacted with a derivative of an acid of the general formula:—

35



in which R_1 and R_2 have the same meanings as in claim 1, and with a compound of the general formula:—



in which R_3 , R_4 and Z have the same meanings as in claim 1 and X is a halogen atom on the residue of a sulphuric acid. 40

47. Process according to claim 46, wherein the amino or hydroxyl group in the amino compound is protected during the reaction by a protective group which is subsequently removed. 45

48. Process according to claim 46 or 47, wherein the acid is used in the form of a halide, anhydride or imidazolidine. 50

49. Process according to any of claims 46 to 48, wherein the product obtained is subsequently converted into a pharmacologically compatible salt.

50. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified. 55

51. Compounds according to claim 1, whenever prepared by the process according to any of claims 46 to 50. 60

52. Pharmaceutical compositions, comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

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