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ALKANOLAMINE DERIVATIVES

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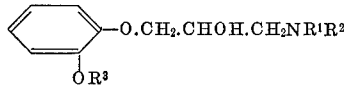
ABSTRACT OF THE DISCLOSURE

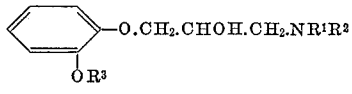
Alkanolamine derivatives of the formula:



wherein R^1 stands for hydrogen or for an alkyl radical, wherein R^2 stands for an alkyl, hydroxyalkyl or cycloalkyl radical, and wherein R^3 stands for an alkyl radical of 2 or more carbon atoms, or for a haloalkyl, cycloalkyl or alkenyl radical, and the aldehyde condensation products and the esters thereof, and the salts thereof. These compounds possess β-adrenergic blocking activity.

This invention relates to new alkanolamine derivatives which possess β-adrenergic blocking activity, for example such activity in cats, and which are therefore likely to be useful in the treatment or prophylaxis of coronary artery diseases, for example angina pectoris and cardiac arrhythmias, and in the treatment of hypertension and phaeochromocytoma, in man.

According to the invention, therefore, we provide new alkanolamine derivatives of the formula:



wherein R^1 stands for hydrogen or for an alkyl radical, wherein R^2 stands for an alkyl, hydroxyalkyl or cycloalkyl radical, and wherein R^3 stands for an alkyl radical of 2 or more carbon atoms, or for a haloalkyl, cycloalkyl or alkenyl radical, and the aldehyde condensation products and the esters thereof, and the salts thereof.

It is to be understood that the above definition of alkanolamine derivatives encompasses all possible stereoisomers thereof, and mixtures thereof.

As a suitable value for R^1 when it stands for an alkyl radical there may be mentioned, for example, an alkyl radical of not more than 6 carbon atoms, for example the methyl, ethyl or isopropyl radical.

As a suitable value for R^2 when it stands for an alkyl or hydroxyalkyl radical there may be mentioned, for example an alkyl or hydroxyalkyl radical of not more than 10 carbon atoms, for example the methyl, ethyl, n-propyl, isopropyl, s-butyl, t-butyl, 1-methyloctyl or 2-hydroxy-1,1-dimethylethyl radical.

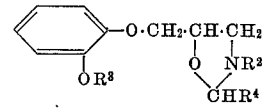
As a suitable value for R^2 or R^3 when it stands for a cycloalkyl radical there may be mentioned, for example, a cycloalkyl radical of not more than 6 carbon atoms, for example the cyclopentyl radical.

As a suitable value for R^3 when it stands for an alkyl radical of 2 or more carbon atoms there may be mentioned, for example, an alkyl radical of at least 2 and not more than 10 carbon atoms, for example the ethyl, isobutyl or n-heptyl radical.

As a suitable value for R^3 when it stands for a haloalkyl radical there may be mentioned, for example, an alkyl radical of not more than 10 carbon atoms bearing one or more fluorine, chlorine or bromine atoms, for example the 2,2-dichloro-1,1-difluoroethyl radical.

As a suitable value for R^3 when it stands for an alkenyl radical there may be mentioned, for example, an alkenyl radical of not more than 6 carbon atoms, for example the allyl radical.

It is to be understood that by the expression "aldehyde condensation products of the alkanolamine derivatives" we mean the oxazolidine derivatives of the formula:



wherein R^2 and R^3 have the meanings stated above, and wherein R^4 stands for hydrogen or for an alkyl or aryl radical, and the salts thereof, which are derived from the alkanolamine derivatives of the invention of the stated formula wherein R^1 stands for hydrogen.

As a suitable value for R^4 when it stands for an alkyl or aryl radical there may be mentioned, for example, an alkyl or aryl radical of not more than 10 carbon atoms, for example the isopropyl or phenyl radical.

As suitable esters of the alkanolamine derivatives there may be mentioned, for example, O-esters derived from a saturated or unsaturated aliphatic carboxylic acid, for example such an acid of not more than 20 carbon atoms, for example acetic, palmitic, stearic or oleic acid, or O-esters derived from an aromatic carboxylic acid, for example such an acid of not more than 10 carbon atoms, for example benzoic acid.

As suitable salts of the alkanolamine derivative, the aldehyde condensation products thereof and the esters thereof there may be mentioned acid-addition salts, for example salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates or sulphates, or salts derived from organic acids, for example oxalates, lactates, tartrates, acetates, salicylates, citrates, benzoates, β-naphthoates, adipates or 1,1'-methylene-bis(2-hydroxy-3-naphthoates), or salts derived from acidic synthetic resins, for example sulphonated polystyrene resins, for example "Zeo-Karb" 225 ("Zeo-Karb" is a trademark). Relatively insoluble salts, for example the 1,1'-methylene-bis-(2-hydroxy-3-naphthoates), have the advantage that they afford prolonged blood levels of the salt when it is used as a medicament.

Particular new alkanolamine derivatives of the invention are, for example,

1-[2-(2,2-dichloro-1,1-difluoroethoxy)phenoxy]-3-isopropylamino-2-propanol;
1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol;
1-(2-ethoxyphenoxy)-3-t-butylamino-2-propanol;
1-(2-ethoxyphenoxy)-3-n-propylamino-2-propanol;
1-(2-ethoxyphenoxy)-3-cyclopentylamino-2-propanol;
1-(2-ethoxyphenoxy)-3-(2-hydroxy-1,1-dimethylethylamino)-2-propanol;
1-(2-ethoxyphenoxy)-3-methylamino-2-propanol;
1-(2-allyloxyphenoxy)-3-isopropylamino-2-propanol;
1-(2-allyloxyphenoxy)-3-t-butylamino-2-propanol;
1-(2-n-heptyloxyphenoxy)-3-isopropylamino-2-propanol;
1-(2-isobutoxyphenoxy)-3-isopropylamino-2-propanol;
1-(2-cyclopentyloxyphenoxy)-3-isopropylamino-2-propanol and
1-(2-cyclopentyloxyphenoxy)-3-cyclopentylamino-2-propanol

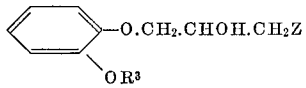
and the aldehyde condensation products and the esters thereof, and the salts thereof, and of these, particularly valuable and preferred compounds are

1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol;
1-(2-ethoxyphenoxy)-3-t-butylamino-2-propanol;
1-(2-allyloxyphenoxy)-3-isopropylamino-2-propanol;

1-(2-allyloxyphenoxy)-3-t-butylamino-2-propanol and 1-(2-isobutoxyphenoxy)-3-isopropylamino-2-propanol

and the salts thereof.

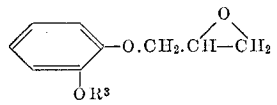
According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the interaction of a halogeno compound of the formula:



wherein Z stands for a halogen atom and wherein R^3 has the meaning stated above, with an amine of the formula NHR^1R^2, wherein R^1 and R^2 have the meanings stated above.

As a suitable value for Z there may be mentioned, for example, a chlorine or bromine atom. The interaction may conveniently be accelerated or completed by the application of heat, and it may be carried out in an inert diluent or solvent, for example methanol.

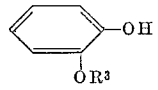
According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the interaction of an epoxide of the formula:



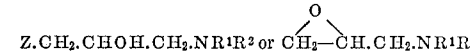
wherein R^3 has the meaning stated above, with an amine of the formula NHR^1R^2, wherein R^1 and R^2 have the meanings stated above.

The interaction involving an epoxide may conveniently be accelerated or completed by the application of heat, and it may be carried out in an inert diluent or solvent, for example methanol or ethanol.

According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the interaction of a compound of the formula:



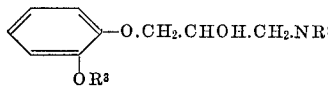
wherein R^3 has the meaning stated above, with a compound of the formula:



wherein R^1, R^2 and Z have the meanings stated above.

The last-named interaction may conveniently be carried out in the presence of an acid-binding agent, for example sodium hydroxide. Alternatively, an alkali metal derivative of the phenol reactant, for example the sodium or potassium derivative, may be used as starting material. The interaction may be carried out in a diluent or solvent, for example ethanol, and it may be accelerated or completed by the application of heat.

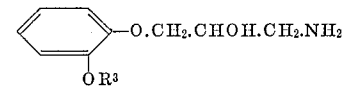
According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention wherein R^1 stands for hydrogen which comprise the hydrogenolysis of a compound of the formula:



wherein R^2 and R^3 have the meanings stated above and wherein R^5 stands for a hydrogenolysable radical, or a salt thereof.

As a suitable value for R^5 there may be mentioned, for example, the benzyl radical. The hydrogenolysis may be effected, for example, by catalytic hydrogenation, for example hydrogenation in the presence of a palladium-on-charcoal catalyst, in an inert diluent or solvent, for example ethanol. The hydrogenolysis is preferably effected in the presence of an acidic catalyst, for example hydrochloric acid.

According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention wherein R^1 stands for hydrogen and wherein R^2 stands for a radical of the formula $—CHR^6R^7$, wherein R^6 stands for hydrogen or for an alkyl radical and R^7 stands for an alkyl or hydroxyalkyl radical, or wherein R^6 and R^7 are joined together with the adjacent carbon atom to form a cycloalkyl radical, which comprises the interaction of an amino derivative of the formula:

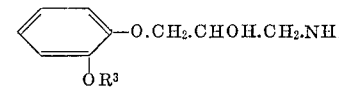


wherein R^3 has the meaning stated above, with a carbonyl compound of the formula $R^6.CO.R^7$ wherein R^6 and R^7 have the meanings stated above, under reducing conditions.

Suitable reducing conditions are those provided by the presence of hydrogen and a hydrogenation catalyst, for example platinum, in an inert diluent or solvent, for example ethanol, and/or, in the case where, in the said carbonyl compound used as starting material, R^6 stands for an alkyl radical, in an excess of the carbonyl compound used as starting material; or by the presence of an alkali metal borohydride, for example sodium borohydride, in an inert diluent or solvent, for example ethanol or aqueous methanol, and/or in an excess of the carbonyl compound used as starting material.

It is to be understood that the said amino derivative may be generated in situ by, for example, reduction of the corresponding α-diazoketone, α-azidoketone, α-hydroxyiminoketone, α-nitroketone, α-nitro-alcohol, cyanhydrin or acyl cyanide.

According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the interaction of an amino derivative of the formula:

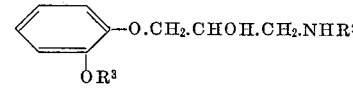


wherein R^1 and R^3 have the meanings stated above, or an ester thereof, or a salt thereof, with a compound of the formula R^2Y, wherein R^2Y stands for a reactive ester derived from an alcohol of the formula R^2OH, wherein R^2 has the meaning stated above.

As a suitable value for Y there may be mentioned, for example, the chlorine, bromine, or iodine atom, the toluene-p-sulphonyloxy radical or a radical of the formula: $—OSO_2OR^2$, wherein R^2 has the meaning stated above. A particularly suitable compound of the formula R^2Y is isopropyl bromide.

The interaction may conveniently be carried out in the presence of a base, for example an inorganic base, for example sodium carbonate, and in the presence of a diluent or solvent, for example ethanol. The interaction may conveniently be carried out at an elevated temperature, for example at a temperature of between 100° C. and 200° C., for example at about 130° C.

According to a further feature of the invention we provide a process for the manufacture of oxazolidine derivatives of the alkanolamines of the invention which comprises the interaction of a compound of the formula:



wherein R^2 and R^3 have the meanings stated above, or a salt thereof, with an aldehyde of the formula R^4CHO, wherein R^4 has the meaning stated above.

The said interaction may be carried out in a diluent or solvent, for example ethanol, benzene, toluene or xylene, optionally in the presence of a catalyst, for example hydrochloric acid, acetic acid or iodine, and it may be accelerated or completed by the application of heat. The water formed during the reaction may be removed by azeotropic distillation using a suitable solvent, for example benzene, toluene or xylene as entraining agent, or it may be removed by means of a dehydrating agent, for example anhydrous potassium carbonate.

According to a further feature of the invention we provide a process for the manufacture of alkanolamine esters of the invention which comprises the interaction of the corresponding alkanolamine derivative or a salt thereof with an acylating agent.

As suitable acylating agents there may be mentioned acid halides or anhydrides derived from saturated or unsaturated aliphatic carboxylic acids of from aromatic carboxylic acids, for example acetyl chloride, acetic anhydride or benzoyl chloride. The acylation may be carried out in a diluent or solvent, which, in the case where an acid anhydride is used as acylating agent, may conveniently be the acid from which the anhydride is derived.

It is to be understood that when R^1 stands for hydrogen, the alkanolamine derivative must be present as a salt thereof, in order that acylation of the nitrogen atom may be prevented.

The invention is illustrated but not limited by the following examples in which the parts are by weight:

EXAMPLE 1

A mixture of 4 parts of 1-chloro-3-[2-(2,2-dichloro-1,1-difluoroethoxy)phenoxy]-2-propanol and 28 parts of isopropylamine is heated in a sealed vessel at 120° C. for 10 hours. The vessel is cooled and opened, the contents are filtered and the filtrate is evaporated to dryness on a steam bath. The solid residue is crystallised from ethyl acetate and there is thus obtained 1-[2-(2,2-dichloro-1,1-difluoroethoxy)phenoxy]-3-isopropylamine - 2-propanol hydrochloride as white needles, M.P. 152–153° C.

The 1-chloro-3-[2-(2,2-dichloro - 1,1 - difluoroethoxy) phenoxy]-2-propanol is prepared in the following manner:

A mixture of 12.8 parts of 2-(2,2-dichloro-1,1-difluoroethoxy)phenol, 25 parts of epichlorohydrin and 0.05 part of piperidine is heated on a steam bath for 16 hours. The excess of epichlorohydrin is removed by evaporation under reduced pressure (40 mm.) and the residue is vacuum-distilled to give a colourless oil, B.P. 122–125° C./0.1 mm. A solution of the above oil in 75 parts of chloroform is shaken twice with 55 parts of concentrated hydrochloric acid, twice with 50 parts of water, dried and filtered and the chloroform is removed by distillation. The residue consists of 1-chloro-3-[2-(2,2-dichloro-1,1-difluoroethoxy)phenoxy]-2-propanol.

The 2-(2,2-dichloro-1,1-difluoroethoxy)phenol is prepared in the following manner:

220 parts of catechol are dissolved in a solution of 100 parts of sodium hydroxide pellets in 600 parts of water and 200 parts of dioxan. The solution is stirred and cooled to 5° C. while a solution of 170 parts of 1,1-difluoro-1,2,2-trichloroethane in 200 parts of dioxane is added dropwise over a period of 5 hours. The mixture is stirred at 20° C. for 16 hours, and is then acidified with concentrated hydrochloric acid until the pH falls below 5. The mixture is then steam distilled until no further trace of oil is visible in the distillate. The lower oily layer is then separated, dried and filtered. The oil is then fractionally distilled under reduced pressure to give a major fraction of a colourless oil, B.P. 73–80° C./3 mm., M.P. 7° C., which consists of 2-(2,2-dichloro-1,1-difluoroethoxy)phenol.

EXAMPLE 2

A solution of 15 parts of 1-chloro-3-(2-ethoxyphenoxy)-2-propanol in 14 parts of isopropylamine is heated in a sealed vessel at 110° C. for 10 hours. The excess of isopropylamine is removed from the mixture by distillation under reduced pressure and the residue is dissolved in 100 parts of aqueous 2 N hydrochloric acid solution. The acidic solution is extracted twice with 50 parts of ether and the extracts are discarded. The acidic solution is basified by the addition of aqueous 10 N sodium hydroxide solution and the basic solution is extracted three times with 50 parts of chloroform each time. The combined chloroform extracts are washed with water, dried over anhydrous magnesium sulphate and the chloroform is removed by distillation. The residue is crystallised from petroleum ether (B.P. 60–80° C.) and there is thus obtained 1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol, M.P. 87–88° C.

The 1-chloro-3-(2-ethoxyphenoxy)-2-propanol used as starting material is obtained in the following manner:

A mixture of 10 parts of o-ethoxyphenol, 17 parts of epichlorohydrin and 0.01 part of piperidine is heated at 95° C. on a steam bath during 18 hours. Excess of epichlorohydrin is removed from the solution by distillation under reduced pressure and the residue is dissolved in 100 parts of chloroform. The chloroform solution is washed successively with 20 parts of water, 20 parts of concentrated hydrochloric acid, 20 parts of water, 20 parts of a saturated aqueous solution of sodium bicarbonate, 20 parts of water and is then dried over anhydrous magnesium sulphate. The chloroform is removed by distillation under reduced pressure and there is thus obtained 1-chloro-3-(2-ethoxyphenoxy)-2-propanol.

EXAMPLE 3

The process described in Example 2 is repeated except that 42 parts of t-butylamine and 42 parts of methanol are used in place of the 14 parts of isopropylamine. The product is isolated as described in Example 2 except that the residual basic oil is dissolved in 100 parts of dry ether. Excess of an ethereal oxalic acid solution is added and the mixture is filtered. The solid residue is crystallised from xylene and there is thus obtained 1-(2-ethoxyphenoxy)-3-t-butylamino-2-propanol hydrogen oxalate,M.P. 97–99° C.

EXAMPLE 4

The process described in Example 2 is repeated except that 45 parts of n-propylamine and 60 parts of methanol are used in place of the 14 parts of isopropylamine. The product is isolated as described in Example 2 and the residue is crystallised from petroleum ether (B.P. 80–100° C.). There is thus obtained 1-(2-ethoxyphenoxy)-3-n-propylamino-2-propanol, M.P. 86.5–87.5° C.

EXAMPLE 5

The process described in Example 2 is repeated except that 45 parts of cyclopentylamine and 60 parts of methanol are used in place of the 14 parts of isopropylamine. The product is isolated as described in Example 2 and the residue is crystallised from petroleum ether (B.P. 60–80° C.). There is thus obtained 3-cyclopentylamino-1-(2- ethoxyphenoxy)-2-propanol, M.P. 87.5–88° C.

EXAMPLE 6

A mixture of 1 part of 2,3-epoxy-1-(2-ethoxyphenoxy) propane, 1 part of 2-amino-2-methylpropan-1-ol and 6 parts of methanol is heated under reflux for 16 hours. The excess amine and the solvent are removed by evaporation and the residue is shaken with a mixture of aqueous 2 N hydrochloric acid and ethyl acetate. The aqueous phase is separated and made alkaline and the mixture is extracted three times with 6 parts of ethyl acetate each time. The combined extracts are dried and evaporated to dryness,

the residual oil is dissolved in ether and ethereal hydrogen chloride solution is added. The mixture is filtered and the solid residue is crystallised from n-butyl acetate. There is thus obtained 1-(2-ethoxyphenoxy)-3-(2-hydroxy-1,1-dimethylethylamino)-2-propanol hydrochloride, M.P. 86–90° C.

The 2,3-epoxy-1-(2-ethoxyphenoxy)propane used as starting material may be obtained as follows:

A mixture of 138 parts of o-ethoxyphenol, 93 parts of epichlorohydrin, 40 parts of sodium hydroxide and 2,000 parts of water is stirred at ambient temperature for 18 hours. The mixture is extracted three times with 2,000 parts of ethyl acetate each time and the combined extracts are dried and evaporated to dryness. The residual oil is distilled and there is thus obtained 2,3-epoxy-1-(2-ethoxyphenoxy)-propane, B.P. 124–128° C./1 mm.

EXAMPLE 7

The process described in Example 6 is repeated except that the 1 part of 2-amino-2-methylpropan-1-ol is replaced by 5 parts of a 10% solution of methylamine in methanol. The product is isolated as described in Example 6 except that the residual oil is crystallised from petroleum ether (B.P. 80–100° C.). There is thus obtained 1-(2-ethoxyphenoxy)-3-methylamino-2-propanol, M.P. 91–92.5° C.

EXAMPLE 8

A mixture of 4 parts of 3-(2-allyloxyphenoxy)-1-chloro-2-propanol, 10 parts of isopropylamine and 20 parts of methanol is heated in a sealed tube at 110° C. for 10 hours. The excess isopropylamine and methanol are removed by evaporation and the residual oil is shaken with aqueous 2 N sodium hydroxide solution and ethyl acetate. The organic phase is separated, dried and evaporated to dryness, and the residue is crystallised from petroleum ether (B.P. 60–80° C.). There is thus obtained 1-(2-allyloxyphenoxy)-3-isopropylamino-2-propanol, M.P. 75.5–76° C.

The 3-(2-allyloxyphenoxy)-1-chloro-2-propanol used as starting material may be prepared as follows:

A mixture of 40 parts of o-allyloxyphenol, 160 parts of epichlorohydrin and 1 part of piperidine is heated at 95–100° C. for 12 hours. The excess epichlorohydrin is removed by distillation under reduced pressure and the residue is shaken with 400 parts of ethyl acetate and 200 parts of water. The organic phase is separated, dried and evaporated to dryness, and there is thus obtained 3-(2-allyloxyphenoxy)-1-chloro-2-propanol.

EXAMPLE 9

A mixture of 2 parts of 1-(2-allyloxyphenoxy)-2,3-epoxypropane, 10 parts of t-butylamine and 30 parts of methanol is heated under reflux for 4 hours. The excess amine and methanol are removed by evaporation and the residue is shaken with ether and aqueous 2 N hydrochloric acid. The aqueous phase is separated, made alkaline and extracted three times with 50 parts of ether each time. The combined ethereal extracts are dried and evaporated to one tenth of their original volume. Ethereal oxalic acid solution is added and the mixture is filtered. The solid residue is crystallised from ethyl acetate and there is thus obtained 1 - (2 - allyloxyphenoxy) - 3 - t - butylamino-2-propanol hydrogen oxalate, M.P. 105–106° C.

The 1-(2-allyloxyphenoxy)-2,3-epoxypropane used as starting material may be obtained as follows:

A mixture of 15 parts of o-allyloxyphenol, 9.3 parts of epichlorohydrin, 4 parts of sodium hydroxide and 350 parts of water is stirred at ambient temperature for 6 hours. The mixture is extracted with 300 parts of ethyl acetate and the extract is dried and evaporated to dryness. The residual oil is distilled and there is thus obtained 1-(2-allyloxyphenol)-2,3-epoxypropane, B.P. 115–122° C./0.7 mm.

EXAMPLE 10

The process described in Example 9 is repeated except that 10 parts of diethylamine are used in place of

the 10 parts of t-butylamine. The product is isolated as described in Example 9 and there is thus obtained 1-(2-allyloxyphenoxy)-3-diethylamino - 2-propanol hydrogen oxalate, M.P. 83–85° C.

EXAMPLE 11

A mixture of 2 parts of 1-chloro-3-(2-n-heptyloxyphenoxy)-2-propanol, 10 parts of isopropylamine and 20 parts of methanol is heated in a sealed tube at 110° C. for 12 hours. The excess amine and methanol are removed by evaporation and the residue is shaken with 30 parts of aqueous 2 N sodium hydroxide solution and 150 parts of ethyl acetate. The organic phase is separated, dried and evaporated to dryness. The residue is crystallised from petroleum ether (B.P. 80–100° C.) and there is thus obtained 3-isopropylamino-1-(2 - n-heptyloxyphenoxy) - 2-propanol, M.P. 77° C.

The 1-chloro-3-(2 - n- heptyloxyphenoxy - 2-propanol used as starting material may be prepared as follows:

55 parts of catechol are dissolved in a solution of 12 parts of sodium in 350 parts of anhydrous methanol, and the mixture is heated under reflux. A solution of 90 parts of n-heptyl bromide in 90 parts of anhydrous methanol is added over 1 hour and the resulting solution is heated under reflux for a further 3 hours. The methanol is removed by evaporation and the residue is shaken with 300 parts of ether and 100 parts of water. The organic phase is separated, dried and evaporated to dryness. The residual oil is distilled and there is thus obtained o-(n-heptyloxy)phenol, B.P. 117–122° C./0.8 mm.

A mixture of 20 parts of o-(n-heptyloxy)phenol, 100 parts of epichlorohydrin and 1 part of piperidine is heated at 95–100° C. for 16 hours. The excess epichlorohydrin is removed by evaporation and the residue is shaken with 400 parts of ethyl acetate and 80 parts of water. The organic phase is separated, dried and evaporated to dryness and there is thus obtained 1-chloro-3-(2-n-heptyloxyphenoxy)-2-propanol.

EXAMPLE 12

The process described in Example 11 is repeated except that 10 parts of n-propylamine are used in place of the 10 parts of isopropylamine. The residue is recrystallised from the petroleum ether (B.P. 80–100° C.) and there is thus obtained 1-(2-n-heptyloxyphenoxy)-3-n-propylamino-2-propanol, M.P. 83° C.

EXAMPLE 13

The process described in Example 11 is repeated except that 10 parts of t-butylamine are used in place of the 10 parts of isopropylamine. The product is isolated as described in Example 11 except that the residual, basic oil is dissolved in 40 parts of anhydrous ether and ethereal oxalic solution is added. The mixture is filtered and the solid residue crystallised from water. There is thus obtained 1-(2-n-heptyloxyphenoxy - 3-t-butylamino - 2-propanol hydrogen oxalate, M.P. 126° C.

EXAMPLE 14

A mixture of 2.35 parts of o-isobutoxyphenol, 12 parts of epichlorohydrin and 0.01 part of piperidine is heated at 90–100° C. for 18 hours. Excess of epichlorohydrin is removed by distillation under reduced pressure and the residual oil is dissolved in 50 parts of chloroform. The chloroform solution is washed successfully with 20 parts of aqueous 11 N-hydrochloric acid, 20 parts of water, 20 parts of aqueous sodium bicarbonate solution and 20 parts of water, and is then dried over anhydrous magnesium sulphate. The chloroform is removed by distillation under reduced pressure and there is thus obtained 1-chloro-3-(2-isobutoxyphenoxy)-2-propanol.

A mixture of this product with 12 parts of isopropylamine is heated in a sealed vessel at 100° C. for 10 hours.

The product is isolated as described in Example 1, and the residue is crystallised from petroleum ether (B.P. 60–80° C.). There is thus obtained 1-(2-isobutoxyphenoxy)-3-isopropylamino-2-propanol, M.P. 84–85° C.

EXAMPLE 15

A mixture of 11 parts of 1-chloro-3-(2-cyclopentyloxyphenoxy)-2-propanol, 100 parts of isopropylamine and 200 parts of methanol is heated in a sealed tube at 110° C. for 12 hours. The excess amine and methanol are removed by evaporation and the residue is shaken with 100 parts of aqueous 2 N sodium hydroxide solution and 100 parts of ethyl acetate. The organic phase is separated, dried and evaporated to dryness, and the residual oil is dissolved in ether. An ethereal solution of oxalic acid is added and the mixture is filtered. The solid residue is crystallised from n-butyl acetate and there is thus obtained 1-(2-cyclopentyloxyphenol - 3-isopropylamino - 2-propanol hydrogen oxalate, M.P. 189–191° C.

The 1-chloro-3-(2-cyclopentyloxyphenoxy - 2-propanol used as starting material may be obtained as follows:

A mixture of 3 parts of o-cyclopentyloxyphenol, 15 parts of epichlorohydrin and 0.2 part of piperidine is heated at 95–100° C. for 16 hours. The excess epichlorohydrin is removed by evaporation and the residue is shaken with 100 parts of ethyl acetate and 30 parts of aqueous 2 N sodium hydroxide solution. The organic phase is separated, dried and evaporated to dryness and there is thus obtained as residue 1-chloro-3-(2-cyclopentyloxyphenoxy)-2-propanol.

EXAMPLE 16

The process described in Example 15 is repeated except that 100 parts of t-butylamine are used in place of 100 parts of isopropylamine. The resulting oxalate is crystallised from n-butyl acetate and there is thus obtained 1-(2-cyclopentyloxyphenoxy) - 3-t-butylamino-2-propanol oxalate, M.P. 166–170° C.

EXAMPLE 17

The process described in Example 15 is repeated except that 10 parts of cyclopentylamine are used in place of 10 parts of isopropylamine. The resulting oxalate is crystallised from ethanol and there is thus obtained 3-cyclopentylamino - 1 - (2-cyclopentyloxyphenoxy)-2-propanol hydrogen oxalate, M.P. 186–187° C.

EXAMPLE 18

A mixture of 20 parts of 1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol, 7 parts of 35% aqueous formalin solution and 600 parts of xylene is heated under reflux for 6 hours, the water formed in the reaction being removed by means of a Dean and Stark water-collecting apparatus. The xylene is removed by evaporation and the residual oil is distilled. There is thus obtained 5-(2-ethoxyphenoxymethyl) - 1 - isopropyloxazolidine, B.P. 135° C./0.2 mm.

EXAMPLE 19

A mixture of 5 parts of 1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol hydrochloride and 50 parts of acetyl chloride is heated under reflux for 6 hours. The excess acetyl chloride is removed by evaporation and the residue is shaken with 50 parts of aqueous 2 N sodium bicarbonate solution and 100 parts of ether. The organic phase is separated, dried and evaporated to dryness. The residual oil is purified by preparative thin-layer chromatography on 1 mm. silica gel plates, the fraction having an R_F value of 0.19 when a mixture of benzene (67% v./v.) and ethyl acetate (33% v./v.) is used as eluant being collected. There is thus obtained 1-(2-ethoxyphenoxymethyl)-2-isopropylaminoethyl acetate as an oil.

EXAMPLE 20

A mixture of 20 parts of 3-amino-1-(2-ethoxyphenoxy)-2-propanol, 14 parts of isopropyl bromide, 12 parts of sodium carbonate and 200 parts of ethanol is heated in a sealed tube at 130° C. for 8 hours. The ethanol is removed by evaporation and the residue is shaken with 60 parts of aqueous 2 N hydrochloric acid and 200 parts of ether. The aqueous phase is separated, made alkaline and extracted with 200 parts of ethyl acetate. The ethyl acetate extract is dried and evaporated to dryness and the residue is crystallised from petroleum ether (B.P. 80–100° C.). There is thus obtained 1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol, M.P. 87–88° C.

The 3-amino-1-(2-ethoxyphenoxy)-2-propanol used as starting material may be prepared as follows:

A mixture of 2 parts of 3-chloro-1-(2-ethoxyphenoxy)-2-propanol, 10 parts of aqueous ammonia solution (specific gravity 0.88) and 20 parts of methanol is heated in a sealed tube at 110° C. for 12 hours. The excess aqueous ammonia solution and methanol are removed by evaporation and the residue is shaken with 30 parts of aqueous 2 N hydrochloric acid and 100 parts of ether. The aqueous acidic solution is made alkaline and is extracted three times with 100 parts of ether each time. The ethereal extract is dried and evaporated to dryness. The residue is dissolved in ether, an ethereal solution of oxalic acid is added, and the mixture is filtered. The solid residue is crystallized from ethanol and there is thus obtained 3-amino-1-(2-ethoxyphenoxy)-2 - propanol hydrogen oxalate, M.P. 148–150° C.

EXAMPLE 21

A mixture of 3 parts of 3-amino-1-(2-ethoxyphenoxy)-2-propanol, 1 part of sodium borohydride, 2 parts of acetone and 20 parts of ethanol is heated under reflux for 4 hours. The ethanol is removed by evaporation and the residue is shaken with 30 parts of aqueous 2 N hydrochloric acid and 100 parts of ether. The aqueous phase is separated, made alkaline and extracted three times with 100 parts of ether each time. The ethereal extracts are combined, dried and evaporated to dryness and the residue is crystallised from petroleum ether (B.P. 60–80° C.). There is thus obtained 1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol, M.P. 87–88° C.

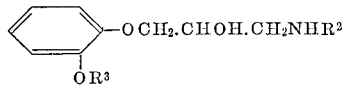
EXAMPLE 22

14 parts of o-ethoxyphenol are added to a solution of 4 parts of sodium hydroxide in 2,000 parts of anhydrous ethanol. To this solution is added a solution of 20 parts of 1-(N-benzyl-N-isopropylamino)-2,3 - epoxypropane in 200 parts of anhydrous ethanol, and the mixture is heated under reflux for 4 hours. The solution is cooled and evaporated to dryness under reduced pressure and the residue is shaken with 500 parts of water and 1,000 parts of ethyl acetate. The organic phase is separated, dried and evaporated to dryness. The residual oil is 3-(N-benzyl-N-isopropylamino) - 1 - (2 - ethoxyphenoxy) 2-propanol.

A mixture of 30 parts of 3-(N-benzyl-N-isopropylamino)-1-(2-ethoxyphenoxy)-2 - propanol, 3 parts of a 10% palladium-on-charcoal catalyst, 30 parts of concentrated hydrochloric acid and 1,000 parts of ethanol is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. The mixture is then filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is shaken with 300 parts of aqueous 2 N hydrochloric acid and 1000 parts of ether. The aqueous phase is separated, made alkaline and extracted three times with 1,000 parts of ether each time. The ethereal extracts are combined, dried and evaporated to dryness and the residue is crystallised from petroleum ether (B.P. 60–80° C.). There is thus obtained 1-(2-ethoxyphenoxy)-3-isopropylamino-2-propanol, M.P. 87–88° C.

What we claim is:

1. A compound selected from the group consisting of alkanolamines of the formula:



wherein R^2 is selected from alkyl of up to 4 carbon atoms, 2-hydroxy-1,1-dimethylethyl and cyclopentyl, and wherein R^3 is selected from 2,2-dichloro-1,1-difluoroethyl and cyclopentyl, and the acid-addition salts thereof.

2. A compound according to claim 1 wherein R^2 is selected from isopropyl and t-butyl.

3. A compound selected from 1-[2-(2,2-dichloro-1,1-difluoro-ethoxy)phenoxy]-3 - isopropylamino - 2 - propanol and the acid-addition salts thereof.

4. A compound according to claim 1 selected from 1-(2-cyclopentyloxyphenoxy) - 3 - isopropylamino-2-propanol and the acid-addition salts thereof.

5. A compound according to claim 1 selected from 1-(2-cyclopentyloxyphenoxy) - 3 - cyclopentylamino-2-propanol and the acid-addition salts thereof.

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