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PATENT SPECIFICATION

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NO DRAWINGS

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Inventors: ALBERT FREDERICK CROWTHER, LESLIE HAROLD SMITH and THOMAS MILLER WOOD.

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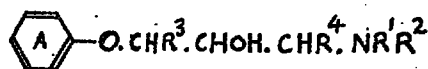
COMPLETE SPECIFICATION

New Alkanolamine Derivatives

5 We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, 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 This invention relates to new alkanolamine derivatives which possess β -adrenergic blocking activity and which are therefore useful in the treatment of prophylaxis of coronary artery disease.

15 According to the invention we provide racemic alkanolamine derivatives of the formula:



20 which is branched at the α -carbon atom, or for the 2-hydroxy-1,1-dimethylethyl or 1-methyl-3-phenylpropyl radical, R^3 and R^4 , which may be the same or different, stand for hydrogen or for alkyl radicals of not more than 5 carbon atoms, and the benzene ring (A) bears a single substituent in the 3- or 4-position only which is a halogen atom, an

alkyl radical containing not more than 4 carbon atoms, an alkoxy, alkylthio, 25 alkanoyl, aralkanoyl, aroyl, aryl, aryl-oxy, alkylaryloxy, arylthio, arylsulphonyl, arylamino, aralkyl, aralkoxy or alkenyl radical each containing not more than 10 carbon atoms, a halogenoalkyl radical containing not more than 5 carbon atoms or a hydroxy or nitro radical, or the benzene ring (A) bears a single substituent in the 2- position only which is a hydroxy, nitro or iodo 30 substituent or an alkanoyl, aralkyl, aroyl, aryl, aryloxy, alkylaryloxy, arylthio, arylsulphonyl, arylamino, aralkyl, or aralkoxy substituent each containing not more than 10 carbon atoms, or the benzene ring (A) bears two, three or four substituents which are selected from the values defined above for the single substituent in the 3- or 4- position only provided that the 2- and 6- positions of the benzene ring (A) are not both substituted; and 35 the carboxylic esters thereof, and the salts thereof.

It is to be understood that the above definition of new alkanolamine derivatives encompasses all possible stereoisomeric racemates 40 thereof, and mixtures thereof.

As a suitable value for R^2 when it stands for

a branched-chain alkyl radical of not more than 10 carbon atoms there may be mentioned, for example, the isopropyl, s-butyl, t-butyl or 1-methyloctyl radical.

5 As a suitable value for R³ or R⁴ when it stands for an alkyl radical of not more than 5 carbon atoms there may be mentioned, for example, the methyl radical.

10 As suitable additional substituents on the benzene ring (A) there may be mentioned, for example, one or more substituents selected from fluorine, chlorine, bromine and iodine atoms, and methyl, ethyl, isopropyl, t-butyl, methoxy, ethoxy, n-butoxy, methylthio, acetyl, benzoyl, hydroxy, trifluoromethyl, phenyl, phenoxy, 4-tolyloxy, phenylthio, phenylsulphonyl, anilino, benzyl, α,α -dimethylbenzyl, benzyloxy and nitro radicals.

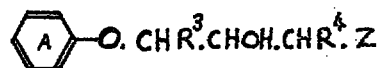
20 As particularly valuable compounds of the invention there may be mentioned, for example, 1-(3-tolyloxy)-, 1-(4-tolyloxy)-, 1-(2,3-dimethylphenoxy)-, 1-(2,4-dimethylphenoxy)-, 1-(3,4-dimethylphenoxy)-, 1-(3,5-dimethylphenoxy)-, 1-(3-ethyl-5-methylphenoxy)-, 1-(3-chlorophenoxy)-, 1-(2,3-dichlorophenoxy)-, 25 1-(3,5-dichlorophenoxy)-, 1-(2,4,5-trichlorophenoxy)-, 1-(3-fluorophenoxy)-, 1-(4-chloro-3-methylphenoxy)-, 1-(3-methoxyphenoxy)-, 1-(2-hydroxyphenoxy)-, 1-(3-nitrophenoxy)-, 1-(3-trifluoromethylphenoxy)-, 1-(2-phenylphenoxy)-, 1-(2-phenoxyphenoxy)-, 1-(3-phenoxyphenoxy)-, 1-(2-benzoyl-5-methoxyphenoxy)-, 1-(4-anilinophenoxy)-, and 1-(2-(4-tolyloxy)phenoxy)- 3-isopropylamino - 2-propanol, and 1-(3,5-dimethylphenoxy)- 3-(1-methyl-3-phenylpropylamino) - 2-propanol, 1-(2,3-dichlorophenoxy) - 3-s-butylamino - 2-propanol, 1-(2-hydroxy-1,1-dimethylethylamino) - 3-(3-tolyloxy)- 40 2-propanol and 1-t-butylamino - 3-(3-tolyloxy) - 2-propanol, and the salts thereof, and the preferred compounds of these are 1-(3-tolyloxy)-, 1-(3,5-dimethylphenoxy)-, 1-(3-chlorophenoxy)-, 1-(2,3-dichlorophenoxy)-, 1-(3,5-dichlorophenoxy)-, 1-(2-phenoxyphenoxy)- and 1-[2-(4-tolyloxy)-phenoxy] - 3-isopropylamino - 2-propanol, and 1-(3,5-dimethylphenoxy) - 3-(1-methyl-3-phenylpropylamino) - 2-propanol and 1-t-butylamino - 3-(3-tolyloxy) - 2-propanol, and the salts thereof.

50 As suitable alkanolamine carboxylic esters there may be mentioned, for example, O-esters derived from a saturated or unsaturated aliphatic carboxylic acid or not more than 20 carbon atoms, for example acetic, palmitic, stearic or oleic acid, or O-esters derived from an aromatic carboxylic acid of not more than 15 carbon atoms, for example benzoic acid.

60 As suitable salts of the alkanolamines and alkanolamine carboxylic esters there may be mentioned acid-addition salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates, or sulphates, or 65 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 derived from acidic synthetic resins, for example sulphonated polystyrene resins, for example "Zeo-Karb" 225 ("Zeo-Karb" is a Trade Mark). Relatively insoluble salts, for example the 1,1'-methylene-bis-(2-hydroxy-3-naphthoates), have the advantage 70 that they afford prolonged blood levels of the medicament.

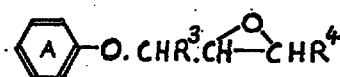
According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the interaction of a halogeno compound of the formula:— 80



wherein Z stands for a chlorine, bromine or iodine atom, and R³, R⁴ and A have the meanings stated above, with an amine of the formula NHR¹R², wherein R¹ and R² have the meanings stated above. 85

As a preferred value for Z there may be mentioned the 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. 90

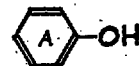
According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the interaction of an epoxide of the formula:— 95



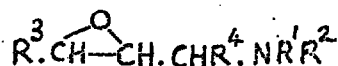
wherein R³, R⁴ and A have the meanings stated above, with an amine of the formula NHR¹R², wherein R¹ and R² have the meanings stated above. 100

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 ethanol. 115

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:— 120



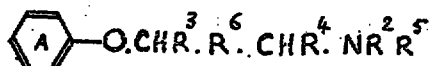
wherein A has the meaning stated above, with a compound of the formula:— 125



wherein R^1 , R^2 , R^3 , R^4 and Z have the meanings stated above.

- 5 The last-named interaction may conveniently be carried out in the presence of an acid-binding agent. Alternatively, an alkali metal derivative of the phenol reactant, for example the sodium or potassium derivative, may be used as starting material.

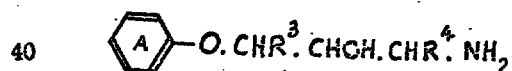
- 10 According to a further feature of the invention we provide a process for the manufacture of the alkanolamine derivatives of the invention which comprises the hydrogenolysis of a compound of the formula:—



- 20 wherein R^2 , R^3 , R^4 and A have the meanings stated above, R^5 stands for a hydrogenolysable radical and R^6 stands for the carbonyl radical (CO).

- 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.

- 30 According to a further feature of the invention we provide a process for the manufacture of those of the alkanolamine derivatives of the invention wherein R^3 stands for a radical of the formula $—CHR^8R^9$, wherein R^8 stands for an alkyl radical of not more than 4 carbon atoms and R^9 stands for an alkyl radical of not more than 8 carbon atoms, or R^8 stands for the methyl radical and R^9 stands for the β -phenylethyl radical, which comprises the interaction of an amino derivative of the formula:—



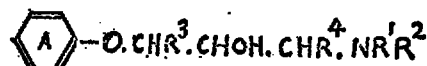
- wherein R^3 , R^4 and A have the meanings stated above, with a carbonyl compound of the formula $R^6.CO.R^9$, wherein R^6 and R^9 have the meanings stated above, under reducing conditions.

- 45 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 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 dil-

uent or solvent, for example aqueous methanol, and/or in an excess of the carbonyl compound used as starting material.

It is to be understood that the said amino derivatives may be generated *in situ* by, for example, reduction of the corresponding α -diazo-ketone, 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 those of alkanolamine derivatives of the invention wherein the benzene ring (A) bears a hydroxy substituent, and optionally may be further substituted as stated above, which comprises the hydrogenolysis of a compound of the formula:—



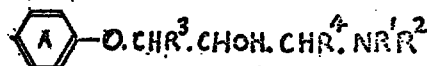
wherein R^1 , R^2 , R^3 and R^4 have the meanings stated above, and wherein the benzene ring (A) bears a substituent of the formula $—OR^7$, wherein R^7 stands for a hydrogenolysable radical, and wherein the benzene ring (A) may optionally be further substituted as stated above.

A suitable value for R^7 is, 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-carbon catalyst, in an inert diluent or solvent, for example ethanol.

According to a further feature of the invention we provide a process for the manufacture of alkanolamine carboxylic esters of the invention which comprises the interaction of the corresponding alkanolamine derivatives 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 not more than 20 carbon atoms, or from aromatic carboxylic acids of not more than 15 carbon atoms, for example 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.

According to a further feature of the invention we provide a process for the manufacture of those of the alkanolamine derivatives of the invention wherein the benzene ring (A) bears an arylsulphonyl substituent, which comprises the oxidation of a compound of the formula:—



wherein R^1 , R^2 , R^3 and R^4 have the meanings stated above and wherein the benzene ring (A)

bears an arylthio substituent.

As a suitable oxidizing agent or procedure there may be mentioned any oxidizing agent or procedure which is known to effect the conversion of an arylthioaryl radical into the corresponding arylsulphonyl radical, for example hydrogen peroxide.

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

EXAMPLE 1

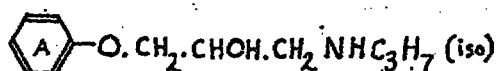
A mixture of 2.03 part of 1-chloro-3-(2,3-dimethylphenoxy)-2-propanol and 15 parts of isopropylamine is heated in a sealed vessel at 70–80°C. for 10 hours. The excess isopropylamine is removed by distillation under reduced pressure. The solid residue is stirred together with water, and the mixture is filtered. The solid residue is suspended in water and 2N-hydrochloric acid is added until dissolution is effected. The solution is washed with 50 parts of ether and then made alkaline with 2N-sodium hydroxide solution, and the resulting mixture is filtered. The solid residue is washed with water, dried, and crystallised from petroleum ether (b.p. 60–80°C.) containing a small amount of petroleum ether (b.p. 100–120°C.). There is thus obtained 1-(2,3-dimethylphenoxy)-3-isopropylamino-2-propanol, m.p. 110–112°C.

The 1-chloro-3-(2,3-dimethylphenoxy)-2-propanol used as starting material may be obtained as follows:—

A mixture of 12.2 parts of 2,3-xyleneol, 25 parts of epichlorohydrin and 0.25 part of pi-

peridine is heated at 90°C. for 6 hours. Excess epichlorohydrin is removed by distillation under reduced pressure. The residue is cooled, dissolved in an equal volume of chloroform, and the solution is shaken with excess concentrated hydrochloric acid. The mixture is separated, the chloroform layer is washed with water until the washings are acid-free, dried over anhydrous sodium sulphate, and filtered. After removal of the solvent by distillation under reduced pressure, the residue is fractionally distilled *in vacuo*. There is thus obtained 1-chloro-3-(2,3-dimethylphenoxy)-2-propanol, b.p. 118°C. at 0.22 mm.

The above procedure is repeated using the appropriate chlorohydrins and amines as starting materials and in a similar manner there are obtained the compounds listed in the following table. Except in the case of the hydrochloride of 1-(2-chloro-4-methylphenoxy)-3-isopropylamino-2-propanol, the acid-addition salts described are obtained by the addition of an ethereal solution of the appropriate acid to an ethereal solution of the base, followed by filtration of the resulting mixture and crystallisation of the solid residue from the indicated solvent or solvent mixture. By contrast, the hydrochloride mentioned above is obtained by suspending the crude base in water, strongly acidifying the suspension with 10N-hydrochloric acid and allowing the resulting solution to stand. The corresponding hydrochloride crystallises out and is filtered off and crystallised from the indicated solvent or solvent mixture.



	Base or Salt	m.p. (°C.)	Crystallisation solvent(s)
3-tolyl	base	79	mixture of pet. ether 40°C./60°C. and 60°C./80°C.
3-tolyl	hydrochloride	121–122	ethyl acetate/ethanol
4-tolyl	base	91–92	cyclohexane
2,4-dimethylphenyl	base	76–77	pet. ether 60°C./80°C.
2,5-dimethylphenyl	base	68–69	pet. ether 60°C./80°C.

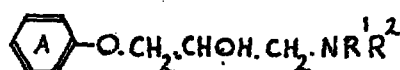
	Base or Salt	m.p. (°C.)	Crystallisation solvent(s)
3,4-dimethylphenyl	hydrochloride	148—149	ethyl acetate/ethanol
3,5-dimethylphenyl	base	108—109	cyclohexane
2,4-di-t-butylphenyl	hydrochloride	191—192	ethyl acetate
2-isopropyl-5-methylphenyl	hydrochloride	159—160	ethyl acetate
2-t-butyl-5-methylphenyl	hydrochloride	175—176	ethyl acetate/ethanol
3-ethyl-5-methylphenyl	base	86—87	pet. ether 60°C./80°C.
4-isopropylphenyl	hydrogen oxalate	179—180	ethyl acetate/ethanol
3-chlorophenyl	base	88—89	pet. ether 60°C./80°C.
4-chlorophenyl	base	99—100	cyclohexane
2,3-dichlorophenyl	base	96—97	cyclohexane
2,4-dichlorophenyl	base	90—91	cyclohexane
2,5-dichlorophenyl	base	83	cyclohexane
3,4-dichlorophenyl	base	124—125	cyclohexane
3,5-dichlorophenyl	base	117—118	cyclohexane
2,4,5-trichlorophenyl	base	114—115	cyclohexane
3-bromophenyl	base	94—95	cyclohexane
4-chloro-3-methylphenyl	base	119	cyclohexane
3-chloro-4-methylphenyl	base	128—129	pet. ether 80°C./100°C.
4-chloro-3,5-dimethylphenyl	base	142	cyclohexane
3-methoxyphenyl	base	72—73	cyclohexane
4-methoxyphenyl	base	82—83	cyclohexane
4-methoxy-2-methylphenyl	hydrogen oxalate	162—163	ethyl acetate/ethanol
3-t-butyl-4-methoxyphenyl	base	95	pet. ether 100°C./120°C.
4-n-butoxyphenyl	base	72—73	cyclohexane
3-nitrophenyl	base	110—111	ethyl acetate

	Base or Salt	m.p. (°C.)	Crystallisation solvent(s)
4-nitrophenyl	hydrogen oxalate	230—232	dimethylformamide
3-trifluoromethylphenyl	hydrogen oxalate	135—136	ethyl acetate/ether
4-acetylphenyl	base	88	cyclohexane
4-biphenyl	base	113—114	cyclohexane
2-biphenyl	base	67—68	cyclohexane
2-hydroxyphenyl	picrate	207—208	aqueous ethanol
2-chloro-4-methylphenyl	hydrochloride	165—166	ethylacetate/ethanol
4-anilinophenyl	base	136	ethyl acetate
2-phenylthiophenyl	hydrochloride	76—78	2N-hydrochloric acid
2-nitrophenyl	picrate	157—158	water
2-iodophenyl	base	99—99.5	cyclohexane

EXAMPLE 2

In a similar manner to that described in Example 1 and using the appropriate chlorohydrin and amine, followed, where desired, by conversion of the resulting base into the acid-

addition salt, there are obtained the compounds listed in the following table (the hydrochlorides are obtained using the procedure involving ethereal hydrochloric acid described in Example 1).



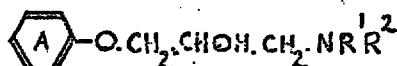
	R ¹	R ²	Base or Salt	m.p. (°C.)	Crystallisation solvent(s)
3-tolyl	H	t-butyl	oxalate	204—205	ethyl acetate/ethanol
3-tolyl	H	s-butyl	hydrochloride	159	ethyl acetate/ethanol
2,3-dichlorophenyl	H	s-butyl	hydrochloride	159—160	ethyl acetate/ethanol
3-tolyl	H	2-hydroxy-1,1-dimethylethyl	hydrogen oxalate	85—86	aqueous ethanol
4-chloro-3-methylphenyl	H	2-hydroxy-1,1-dimethylethyl	hydrogen oxalate	192	aqueous ethanol

EXAMPLE 3

A mixture of 1.94 parts of 1,2-epoxy-3-(3-ethoxyphenoxy)propane and 25 parts of isopropylamine is heated under reflux for 2 hours. Excess isopropylamine is removed by distillation under reduced pressure. The residue is dissolved in 2N-hydrochloric acid. The solution is washed twice with 50 parts of ether and then basified with 2N-sodium hydroxide solution. The mixture is extracted twice with 100 parts of ether. The combined ether extracts are washed with 100 parts of water,

dried over anhydrous magnesium sulphate, and filtered. The solvent is removed by distillation. The residue is dissolved in 20 parts of ether, and ethereal oxalic acid is added until precipitation is complete. The mixture is filtered and the solid residue is crystallised from dimethylformamide. There is thus obtained 1 - (3 - ethoxyphenoxy) - 3 - isopropylamino - 2 - propanol oxalate, m.p. 155—156°C.

In a similar manner using the appropriate starting materials there are obtained the compounds listed in the following table:—



	R ¹	R ²	Base or Salt	m.p. (°C.)	Crystallisation solvent(s)
3-fluorophenyl	H	isopropyl	base	88—89	cyclohexane
3,5-dimethoxyphenyl	H	isopropyl	hydrogen oxalate	149—150	ethyl acetate/ethanol
2,3-dimethoxyphenyl	H	isopropyl	base	77—79	pet. ether 60/80°C.
3-phenoxyphenyl	H	isopropyl	hydrochloride	119—121	ethyl acetate
2-benzoyl-5-methoxyphenyl	H	isopropyl	hydrogen oxalate	195	n-propanol
2-benzylphenyl	H	isopropyl	hydrochloride	106—107	ethyl acetate

EXAMPLE 4

A mixture of 10.8 parts of *m*-cresol, 25 parts of epichlorohydrin, 4.8 parts of sodium hydroxide and 100 parts of water is stirred at ambient temperature for 24 hours. The mixture is neutralised with glacial acetic acid and then extracted twice with 200 parts of chloroform. The combined chloroform extracts are washed three times with an equal volume of water, and then dried over anhydrous magnesium sulphate. The mixture is filtered and the solvent is removed by distillation under reduced pressure. The residue consists of 1,2-epoxy-3-(3-tolyloxy)propane. This is refluxed together with 60 parts of isopropylamine for 1 hour, and the mixture is then kept at ambient temperature for 18 hours. Excess isopropylamine is removed by distillation. The residue is suspended in 500 parts of water, and concentrated hydrochloric acid is added until dissolution is effected. The solution is washed twice with an equal volume of ether. The aqueous solution is basified with 2N-sodium hydroxide solution, and the resulting mixture is filtered

The solid residue is washed with water, dried and crystallised from cyclohexane. There is thus obtained 1-isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol, m.p. 79°C.

In a similar manner by use of 4 - benzyloxyphenol in place of *m*-cresol there is obtained 1 - (4 - benzyloxyphenoxy) - 3 - isopropylamino - 2 - propanol, m.p. 100—101°C. (crystallised from cyclohexane).

EXAMPLE 5

A mixture of 2.4 parts of 1,2-epoxy-3-(2-phenoxyphenoxy)propane and 10 parts of isopropylamine is heated under reflux for 1 hour. The excess isopropylamine is removed by distillation under reduced pressure. The oily residue is dissolved in 50 parts of 2N-hydrochloric acid, decolourising charcoal is added and the mixture is refluxed for 10 minutes. The mixture is filtered whilst hot, and the filtrate is cooled. The resulting mixture is filtered and the solid residue is crystallised from ethyl acetate. There is thus obtained 1-isopropylamino - 3 - (2 - phenoxyphenoxy) - 2 - propanol hydrochloride, m.p. 120—122°C.

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

To a solution of 18.6 parts of 2-phenoxyphenol and 4.8 parts of sodium hydroxide in 100 parts of water there are added dropwise, below 20°C., 11.6 parts of epichlorohydrin. The mixture is stirred at ambient temperature for 18 hours and is then extracted twice with 50 parts of chloroform. The combined chloroform extracts are dried with anhydrous magnesium sulphate and then evaporated under reduced pressure. The oily residue consists of 1,2-epoxy-3-(2-phenoxyphenoxy)propane.

In a similar manner using the appropriate starting materials there are obtained 1-isopropylamino - 3 - [2 - (4 - tolyloxy) - phenoxy] - 2 - propanol hydrochloride, m.p. 117—119°C. (crystallised from a mixture of ethyl acetate and ether) and 1 - [2 - (α,α - dimethylbenzyl) - 4 - methylphenoxy] - 3 - isopropylamino - 2 - propanol hydrochloride, m.p. 185—186°C. (crystallised from a mixture of ethyl acetate and ethanol).

EXAMPLE 6

2.4 Parts of 1 - (2 - benzylphenoxy) - 2,3 - epoxypropane and 10 parts of isopropylamine are heated together under reflux for 1 hour. The mixture is cooled, and 20 parts of 2N-hydrochloric acid are added. The precipitate thus formed is separated by decantation and stirred together with 20 parts of 2N-sodium hydroxide solution. The mixture is then extracted with 50 parts of ether and the ethereal extract is dried over anhydrous magnesium sulphate. Ethereal hydrogen chloride is added to the dry ethereal solution until precipitation is complete. The mixture is filtered and the solid residue is washed with ether and then crystallised from ethyl acetate. There is thus obtained 1 - (2 - benzylphenoxy) - 3 - isopropyl - amino - 2 - propanol hydrochloride, m.p. 106—107°C.

EXAMPLE 7

A mixture of 2.84 parts of 1 - (2 - benzoyl - 5 - methoxyphenoxy) - 2,3 - epoxypropane and 10 parts of isopropylamine are heated together under reflux for 1 hour. The mixture is evaporated to dryness under reduced pressure. The residue is acidified with 25 parts of 2N-hydrochloric acid and washed with 50 parts of ether. The aqueous solution is added to 50 parts of 2N - sodium hydroxide solution at 0°C., and the mixture is then extracted with 50 parts of ether. The ethereal extract is dried over anhydrous magnesium sulphate. The dry ethereal solution is added to a solution of 1.26 parts of oxalic acid in 5 parts of acetone. The mixture is filtered and the solid residue is crystallised from n-propanol. There is thus obtained 1 - (2 - benzoyl - methoxyphenoxy) - 3 - isopropylamino - 2 - propanol hydrogen oxalate, m.p. 195°C.

EXAMPLE 8

A mixture of 2 parts of 1 - amino - 3 -

(3 - tolyloxy) - 2 - propanol hydrochloride, 40 parts of methanol and 10 parts of acetone is adjusted to pH 7 with 2N-sodium hydroxide solution. The solution is heated under reflux for 10 minutes. It is then cooled in ice, and 2 parts of sodium borohydride are added. The mixture is kept at ambient temperature for 18 hours, and is then poured into a mixture of ice and hydrochloric acid. The solution is basified with sodium hydroxide solution and extracted with ether. The ethereal extract is washed twice with an equal volume of water, dried over anhydrous magnesium sulphate, and filtered. The solvent is removed by distillation. The residue is re-dissolved in 10 parts of ethanol, and ethereal hydrochloric acid is added until precipitation is complete. The mixture is filtered and the solid residue is crystallised from an ethyl acetate-ethanol mixture (10:1). There is thus obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 121—122°C.

The 1 - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride used as starting material may be obtained as follows:—

A mixture of 16.4 parts of 1,2-epoxy - 3 - (3 - tolyloxy) - propane, 9.9 parts of succinimide, 0.5 part of pyridine and 75 parts of ethanol is heated for 4 hours under reflux. The solution is cooled and the resulting mixture is filtered. The solid residue is washed with ethanol and crystallised from a mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.). There is thus obtained 1 - succinimido - 3 - (3 - tolyloxy) - 2 - propanol, m.p. 106—107°C.

A mixture of 10 parts of 1 - succinimido - 3 - (3 - tolyloxy) - 2 - propanol and 40 parts of 10N-hydrochloric acid is heated at 100°C. for 8 hours. The hydrochloric acid is then removed by distillation under reduced pressure. The solid residue is dissolved in 250 parts of water and the resulting solution is washed twice with an equal volume of ether. The aqueous solution is evaporated to dryness by distillation under reduced pressure, and the solid residue is crystallised from a mixture of ethyl acetate and ethanol. There is thus obtained 1 - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride which melts to an opaque semi-solid at 128—129°C. and to a clear liquid at 272°C.

EXAMPLE 9

To a solution of 1 part of 1 - (N - benzyl - N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol in 10 parts of ether there is added an ethereal solution of hydrogen chloride until precipitation is complete. The mixture is evaporated to dryness, and the residue is dissolved in 15 parts of ethanol. 10 Parts of palladium-on-charcoal catalyst are added to the solution, and the mixture is shaken at ambient temperature and atmospheric pressure in an atmosphere of hydrogen for 6 hours. The

mixture is filtered, and the solvent is removed from the filtrate by distillation under reduced pressure. The solid residue is crystallised from a mixture of ethyl acetate and ethanol (10:1 by weight). There is thus obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 121—122°C.

The 1 - (N - benzyl - N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol may be obtained as follows:—

A mixture of 14.9 parts of N - benzyl - N - isopropylamine and 10.33 parts of epichlorohydrin is heated and stirred at 85—90°C. for 4 hours and then kept at ambient temperature for 18 hours. The mixture is then shaken together with 50 parts of 20% sodium carbonate solution. The mixture is separated and the organic phase is dissolved in 200 parts of ether. This solution is washed with cold water, dried over anhydrous potassium carbonate, and filtered. After removal of the solvent by distillation, the residue is fractionally distilled *in vacuo*. There is thus obtained 1 - (N - benzyl - N - isopropylamino) - 3 - chloro - 2 - propanol, b.p. 122—130°C./1.0—1.1 mm. A mixture of 4.8 parts of this chlorohydrin together with a solution of 0.92 part of sodium in 36 parts of ethanol, and 2.2 parts of *m*-cresol is heated in a sealed tube for 10 hours at 100°C. The tube is cooled and the contents are filtered. The filtrate is evaporated to dryness under reduced pressure. The residue is stirred together with 25 parts of 2N - hydrochloric acid and the resulting suspension is washed twice with 50 parts of ether. The supernatant aqueous layer is removed by decantation and the residue is stirred together with 25 parts of 2N - sodium hydroxide solution. The mixture is extracted with 150 parts of ether and the ethereal extract is washed with cold water, dried over anhydrous magnesium sulphate, and filtered. To the filtrate there is added a saturated solution of picric acid in ether until precipitation is complete. The mixture is crystallised and the solid residue is crystallised from aqueous ethanol. There is thus obtained 1 - (N - benzyl - N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol picrate, m.p. 123—125°C. The picrate is suspended in 25 parts of 2N-hydrochloric acid and the suspension is extracted three times with 50 parts of ethyl acetate. The combined ethyl acetate extracts are extracted with 10N-ammonium hydroxide solution, each time with 100 parts, until the ethyl acetate layer is colourless. The ethyl acetate solution is dried over anhydrous magnesium sulphate and the solvent is evaporated under reduced pressure. There is thus obtained 1 - (N - benzyl - N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol.

The 1 - (N - benzyl - N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol may alternatively be obtained as follows:—

A mixture of 10 parts of 1 - (N - benzyl -

N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol and 25 parts of 50% sodium hydroxide solution is stirred and heated at 100°C. for 4 hours. The mixture is cooled and extracted with ether. The ethereal extract is washed with water, dried over anhydrous magnesium sulphate, and filtered. The solvent is removed from the filtrate by distillation under reduced pressure. The residual syrupy material is fractionally distilled *in vacuo*, and there is thus obtained 1 - (N - benzyl - N - isopropylamino) - 2,3 - epoxypropane, b.p. 88—92°C./0.15 mm. A mixture of 4.1 parts of the epoxide, a solution of 0.46 part of sodium in 18 parts of ethanol, and 2.16 parts of *m*-cresol is heated in a sealed tube for 10 hours at 100°C. The 1 - (N - benzyl - N - isopropylamino) - 3 - (3 - tolyloxy) - 2 - propanol is isolated from the reaction mixture in the same manner as that described above.

EXAMPLE 10

A mixture of 2.1 parts of 1 - bromo - 3 - (3 - tolyloxy) - 2 - propanol and 15 parts of isopropylamine is heated in a sealed tube at 100°C. for 6 hours. The product is isolated by a similar procedure to that described in Example 1, and there is obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol, m.p. 79°C. (crystallised from cyclohexane).

The 1 - bromo - 3 - (3 - tolyloxy) - 2 - propanol used as starting material may be obtained as follows:—

A mixture of 9 parts of 3 - tolyloxyacetyl chloride in 150 parts of anhydrous ether is added dropwise over a period of 30 minutes to a cooled (–15°C.) solution of 16.5 parts of diazomethane in anhydrous ether. The reaction mixture is stirred gently during the addition and afterwards for 1 hour. The temperature of the solution is allowed to rise to ambient temperature and the solution is kept at this temperature for 18 hours. The solution is then stirred and cooled to –15°C. and 20 parts of 48% hydrobromic acid are added dropwise. The mixture is separated, and the ethereal layer is washed with an equal volume of 5% aqueous sodium carbonate solution and then twice with an equal volume of water. The ethereal solution is dried (anhydrous magnesium sulphate) and the solvent is then removed by distillation under reduced pressure. The residue is 1 - bromo - 3 - (3 - tolyloxy) - 2 - propanone [characterised as the 2,4-dinitrophenylhydrazone, m.p. 128—130°C. (crystallised from ethanol)]. 2 Parts of this residue are dissolved in 25 parts of methanol, and the solution is cooled to 0°C. 2 Parts of sodium borohydride are added portionwise to the cooled solution and the mixture is kept at ambient temperature for 18 hours. The mixture is poured into a mixture of ice and hydrochloric acid and the resulting acidic solution is extracted three times using an equal volume of chloroform each time. The combined chloro-

form extracts are washed twice with an equal volume of water, dried over anhydrous magnesium sulphate, and then filtered. The chloroform is then removed by distillation under reduced pressure, and there is obtained as the residue 1 - bromo - 3 - (3 - tolyloxy) - 2 propanol.

EXAMPLE 11

A mixture of 2 parts of 3 - chloro - 1 - (3 - tolyloxy) - 2 - butanol and 15 parts of isopropylamine is heated in a sealed vessel at 100°C. for 10 hours. The product is isolated by a similar procedure to that described in Example 1, and there is obtained 3 - isopropyl - amino 1 - (3 - tolyloxy) - 2 - butanol monohydrate, m.p. 78—80°C. (crystallised from aqueous ethanol).

The 3 - chloro - 1 - (3 - tolyloxy) - 2 - butanol used as starting material may be obtained as follows:—

A solution of 10 parts of 3-tolyloxyacetyl chloride in 150 parts of anhydrous ether is added dropwise over a period of 30 minutes to a well-cooled (−15°C.) and gently-stirred solution of 13.6 parts of diazoethane in 300 parts of anhydrous ether. After the addition, the reaction mixture is stirred for one hour at −10°C. The temperature of the solution is then allowed to rise to ambient temperature, and the solution is kept at ambient temperature for 18 hours. The solution is then cooled to −15°C., and anhydrous hydrogen chloride is bubbled through the solution until the evolution of nitrogen ceases. The solution is then washed twice with an equal volume of water, once with an equal volume of 5% sodium carbonate solution, and again with an equal volume of water. The solution is then dried (anhydrous magnesium sulphate). The solvent is removed under reduced pressure giving, as residue, 3 - chloro - 1 - (3 - tolyloxy) - 2 - butanone [characterised as the 2,4 - dinitro - phenylhydrazone, m.p. 118—119°C. (crystallised from ethanol)]. 5 Parts of this residue are dissolved in 25 parts of methanol, and the solution is cooled to 0°C. To the solution 5 parts of sodium borohydride are added in portions, and the resulting mixture is kept at ambient temperature for 4 hours. The mixture is poured into a mixture of ice and hydrochloric acid, and the resulting solution is extracted twice with equal volumes of ether. The combined extracts are washed with an equal volume of water, and dried (anhydrous magnesium sulphate). The solvent is removed by distillation under reduced pressure, and there is obtained as the residue 3 - chloro - 1 - (3 - tolyloxy) - 2 - butanol.

EXAMPLE 12

The procedure described in Example 11 is repeated except that the 3 - chloro - 1 - (3 - tolyloxy) - 2 - butanol is replaced by 1 - chloro - 3 - (3 - tolyloxy) - 2 - butanol, and there is thus obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - butanol oxalate hydrate,

m.p. 98—108°C. (crystallised from a mixture of ethyl acetate and ethanol). This compound is separated into its two diastereoisomers in the following way:—

The compound is heated at 80°C. together with 20 parts of ethyl acetate for 10 minutes, and the hot mixture is then filtered, both the solid residue and the filtrate being retained. The solid residue is crystallised several times from a mixture of ethyl acetate and ethanol until material of constant melting point is obtained. There is thus obtained one diastereoisomer of 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - butanol oxalate, m.p. 151—152°C. The above-mentioned filtrate is cooled and the resulting mixture is filtered. The solid residue is crystallised several times from ethyl acetate until material of constant melting point is obtained, and there is thus obtained the other diastereoisomer of 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - butanol oxalate, m.p. 92—94°C.

The 1 - chloro - 3 - (3 - tolyloxy) - 2 - butanol used as starting material may be obtained by a similar procedure to that described in Example 11 starting from α - (3 - tolyloxy)propionyl chloride and diazomethane, α - (3 - tolyloxy)propionyl chloride itself may be obtained as follows:—

A mixture of 10 parts of α - (3 - tolyloxy)propionic acid and 6.6 parts of thionyl chloride is heated at 60°C. for 4 hours. The mixture is cooled, stirred together with 20 parts of petroleum ether (b.p. 60—80°C.), and filtered. The filtrate is evaporated under reduced pressure and there is obtained, as residue, α - (3 - tolyloxy)propionyl chloride.

EXAMPLE 13

A mixture of 1.09 parts of 1 - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, 1.48 parts of methyl phenethyl ketone, 35 parts of ethanol and 0.1 part of platinum oxide is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure until the uptake of hydrogen ceases. The mixture is filtered, and the filtrate is evaporated to dryness under reduced pressure. The residue is suspended in dilute hydrochloric acid, and the suspension is shaken together with an equal volume of ether. The mixture is filtered and the solid residue is crystallised from ethyl acetate. There is thus obtained 1 - (1 - methyl - 3 - phenylpropylamino) - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 146—151°C.

In a similar manner, but using 2-nonanone in place of methyl phenethyl ketone, there is obtained 1 - (1 - methyloctylamino) - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 110—120°C.

In a similar manner, but using acetone in place of methyl phenethyl ketone, there is obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 121—

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122°C. (crystallised from a mixture of ethyl acetate and ethanol).

EXAMPLE 14

A mixture of 25 parts of 1 - (3,5 - dimethylphenoxy) - 2,3 - epoxypropane and 21 parts of 1 - methyl - 3 - phenylpropylamine is heated at 100°C. for 2 hours. The mixture is cooled and dissolved in 300 parts of ether, and dry hydrogen chloride is passed into the solution until precipitation is complete. The mixture is filtered, the solid residue is suspended in ether, and the suspension is stirred for 24 hours. The mixture is filtered, the solid residue is suspended in ethyl acetate, and the mixture is stirred for 2 hours. The mixture is filtered and there is obtained, as solid residue, crude 1 - (3,5 - dimethylphenoxy) - 3 - (1 - methyl - 3 - phenyl - propylamino) - 2 - propanol hydrochloride, m.p. 118—132° (product A). This product is crystallised from ethyl acetate, and there is obtained a mixture of diastereoisomers of 1 - (3,5 - dimethylphenoxy) - 3 - (1 - methyl - 3 - phenylpropylamine) - 2 - propanol hydrochloride, m.p. 139—142°C.

Product A may be separated into two pure diastereoisomers as follows:—

A mixture of 20 parts of product A and 200 parts of ethyl acetate is heated under reflux for 10 minutes, and the mixture is then filtered while hot. Both the solid residue and the filtrate (B) are retained. The solid residue is crystallised from a mixture of ethyl acetate and ethanol until its melting point is constant. There is thus obtained one diastereoisomer of 1 - (3,5 - dimethylphenoxy) - 3 - (1 - methyl - 3 - phenylpropylamino) - 2 - propanol hydrochloride, m.p. 149—151°C.

The filtrate (B) is allowed to cool to ambient temperature, and the resulting mixture is filtered. The filtrate is cooled to 0°C., and the resulting mixture is filtered. The solid residue is stirred together with 20 parts of 2N-sodium hydroxide solution, and the mixture is extracted with an equal volume of ether. The ethereal extract is washed with water, dried over anhydrous magnesium sulphate, and filtered. The solvent is removed under reduced pressure, 2.5 parts of the residue are dissolved in 100 parts of ether, and a solution of 1.65 parts of oxalic acid in 200 parts of ether is added to the solution. The resulting mixture is filtered, and the solid residue is refluxed with a mixture of ethyl acetate and ethanol for 10 minutes, and then filtered whilst hot. The filtrate is cooled to 0°C., and the resulting mixture is filtered. The filtrate is evaporated to dryness under reduced pressure, the residue is dissolved in 1 part of ethanol and 10 parts of ether are added. The mixture is filtered, and the solid residue is shaken together with 7N-ammonium hydroxide solution until complete dissolution is effected. The solution is extracted with an equal volume of ether, and the ethereal extract is washed with water, dried

over anhydrous magnesium sulphate, and filtered. The filtrate is evaporated to small volume, and ethereal hydrochloric acid is added. The crystalline solid which separates on standing is filtered off and crystallised from ethyl acetate until its melting point is constant. There is thus obtained the other diastereoisomer of 1 - (3,5 - dimethylphenoxy) - 3 - (1 - methyl - 3 - phenylpropylamino) - 2 - propanol hydrochloride, m.p. 136—137°C.

The above procedure for the preparation of a mixture of diastereoisomers of 1 - (3,5 - dimethylphenoxy) - 3 - (1 - methyl - 3 - phenylpropylamino) - 2 - propanol hydrochloride is repeated, except that 49.2 parts of 1,2 - epoxy - 3 - (3 - tolyloxy) - 2 - propane and 4.7 parts of 1 - methyl - 3 - phenylpropylamine are used as starting materials. There is thus obtained a mixture of diastereoisomers of 1 - (1 - methyl - 3 - phenylpropylamino) - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 110—130°C.

EXAMPLE 15

2 Parts of 100 volume hydrogen peroxide are added to a solution of 0.7 part of 1 - isopropylamino - 3 - (2 - phenylthiophenoxy) - 2 - propanol hydrochloride in 4 parts of glacial acetic acid, and the mixture is kept at ambient temperature for 18 hours. The mixture is then basified with 2N-sodium hydroxide solution and extracted with a mixture of 25 parts of ether and 25 parts of ethyl acetate. The extract is dried with anhydrous magnesium sulphate, and to it there is added a solution of oxalic acid in ether until precipitation is substantially complete. The mixture is filtered, and the solid residue is washed with ether and crystallised from n-propanol. There is thus obtained 1 - isopropylamino - 3 - (2 - phenylsulphonylphenoxy) - 2 - propanol hydrogen oxalate, m.p. 184°C. with decomposition.

EXAMPLE 16

A mixture of 3 parts of 1 - (4 - benzyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, 0.1 part of palladium-on-charcoal catalyst, 40 parts of ethanol and 0.1 part of concentrated hydrochloric acid is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure until uptake of hydrogen ceases. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is crystallised from a mixture of ethyl acetate and ethanol, and there is thus obtained 1 - (4 - hydroxyphenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride, m.p. 167—168°C.

EXAMPLE 17

A mixture of 2.2 parts of 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol, 10 parts of acetic acid, and 2 parts of acetic anhydride is kept at ambient temperature for 18 hours. Ice is then added, and the mixture is

basified with ammonium hydroxide solution. The mixture is extracted with 50 parts of ether, and the ethereal extract is dried with anhydrous magnesium sulphate. An ethereal solution of hydrochloric acid is added to the dry ethereal solution until precipitation is complete. The mixture is filtered, and the solid residue is crystallised from a mixture of benzene and ether. There is thus obtained 1 - isopropylaminomethyl - 2 - (3 - tolyloxy)ethyl acetate as its hydrochloride, m.p. 130—132°C.

EXAMPLE 18

A mixture of 2.6 parts of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride and 6 parts of benzoyl chloride is heated for 6 hours at 100°C. The mixture is then cooled and 50 parts of ether are added. The mixture is stirred, the ether is decanted, and a further 50 parts of ether are added. The mixture is again stirred and is then filtered. The solid residue is washed with ether and dried. The solid is crystallised from a mixture of benzene and ether, and there is obtained 1 - isopropylaminomethyl - 2 - (3 - tolyloxy) ethyl benzoate as its hydrochloride, m.p. 118—120°C.

EXAMPLE 19

A solution of 0.25 part of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol in 15 parts of ethyl acetate is added to a solution of 0.2 part of benzoic acid in 10 parts of ether. The mixture is filtered and the solid residue is washed with ether. There is thus obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol benzoate, m.p. 151—152°C. (crystallised from ethyl acetate).

By replacing the benzoic acid in the above example with 0.25 part of β -naphthoic acid there is similarly obtained 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol β -naphthoate, m.p. 113—114°C. (crystallised from a mixture of n-hexane and ethyl acetate).

By replacing the benzoic acid in the above example with 0.2 part of adipic acid there is similarly obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol adipate, m.p. 124—126°C. (crystallised from ethyl acetate).

EXAMPLE 20

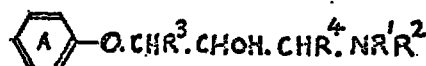
A solution of 0.65 part of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride in 10 parts of water is added to a solution of 1 part of disodium 1,1' - methylene - bis - (2 - hydroxy - 3 - naphthoate) in 10 parts of water. The mixture is stirred and filtered. The solid residue is washed with water, dried and crystallised from a mixture of 10 parts of ethyl acetate and 20 parts of ether. There is thus obtained di - [1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol] 1,1' - methylene - bis - (2 - hydroxy - 3 - naphthoate), m.p. 186—188°C.

EXAMPLE 21

To a solution of 1 part of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride in 10 parts of water there is added a suspension of 10 parts of a sulphonated polystyrene resin ["Zeo-Karb" 225(SCR 9)—"Zeo-Karb" is a Trade Mark] in 40 parts of water. The mixture is stirred for 1 hour at ambient temperature. It is then filtered and the solid residue is washed with water. There is thus obtained a complex salt of 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol with a sulphonated polystyrene resin which has a base content of 13.5%.

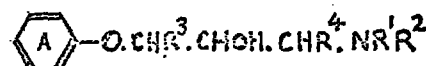
WHAT WE CLAIM IS:—

1. Racemic alkanolamine derivatives of the formula:—



wherein R¹ stands for hydrogen R² stands for an alkyl radical or not more than 10 carbon atoms which is branched at the α -carbon atom, or for the 2 - hydroxy - 1,1 - dimethyl - ethyl or 1 - methyl - 3 - phenylpropyl radical, R³ and R⁴, which may be the same or different, stand for hydrogen or for alkyl radicals of not more than 5 carbon atoms, and the benzene ring (A) bears a single substituent in the 3- and 4- position only which is a halogen atom, an alkyl radical containing not more than 4 carbon atoms, an alkoxy, alkylthio, alkanoyl, aralkanoyl, aroyl, aryl, aryloxy, alkylaryloxy, arylthio, arylsulphonyl, arylamino, aralkyl, aralkoxy or alkenyl radical each containing not more than 10 carbon atoms, a halogenoalkyl radical containing not more than 5 carbon atoms, or a hydroxy or nitro radical, or the benzene ring (A) bears a single substituent in the 2- position only which is a hydroxy, nitro or iodo substituent or an alkanoyl, aralkanoyl, aroyl, aryl, aryloxy, alkylaryloxy, arylthio, arylsulphonyl, arylamino, aralkyl or aralkoxy substituent each containing not more than 10 carbon atoms, or the benzene ring (A) bears two, three or four substituents which are selected from the values defined above for the single substituent in the 3- or 4- position only, provided that the 2- and 6- positions of the benzene ring (A) are not both substituted; and the carboxylic esters thereof; and the salts thereof.

2. Racemic alkanolamine derivatives of the formula:—



wherein R¹ stands for hydrogen; wherein R² stands for an alkyl radical of not more than 10 carbon atoms which is branched at the α -carbon atom, or for the 2 - hydroxy - 1,1 - dimethylethyl or 1 - methyl - 3 - phenyl -

basified with ammonium hydroxide solution. The mixture is extracted with 50 parts of ether, and the ethereal extract is dried with anhydrous magnesium sulphate. An ethereal solution of hydrochloric acid is added to the dry ethereal solution until precipitation is complete. The mixture is filtered, and the solid residue is crystallised from a mixture of benzene and ether. There is thus obtained 1 - isopropylaminomethyl - 2 - (3 - tolyloxy)ethyl acetate as its hydrochloride, m.p. 130—132°C.

EXAMPLE 18

A mixture of 2.6 parts of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride and 6 parts of benzoyl chloride is heated for 6 hours at 100°C. The mixture is then cooled and 50 parts of ether are added. The mixture is stirred, the ether is decanted, and a further 50 parts of ether are added. The mixture is again stirred and is then filtered. The solid residue is washed with ether and dried. The solid is crystallised from a mixture of benzene and ether, and there is obtained 1 - isopropylaminomethyl - 2 - (3 - tolyloxy) ethyl benzoate as its hydrochloride, m.p. 118—120°C.

EXAMPLE 19

A solution of 0.25 part of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol in 15 parts of ethyl acetate is added to a solution of 0.2 part of benzoic acid in 10 parts of ether. The mixture is filtered and the solid residue is washed with ether. There is thus obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol benzoate, m.p. 151—152°C. (crystallised from ethyl acetate).

By replacing the benzoic acid in the above example with 0.25 part of β -naphthoic acid there is similarly obtained 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol β -naphthoate, m.p. 113—114°C. (crystallised from a mixture of n-hexane and ethyl acetate).

By replacing the benzoic acid in the above example with 0.2 part of adipic acid there is similarly obtained 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol adipate, m.p. 124—126°C. (crystallised from ethyl acetate).

EXAMPLE 20

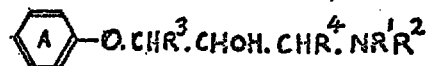
A solution of 0.65 part of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride in 10 parts of water is added to a solution of 1 part of disodium 1,1' - methylene - bis - (2 - hydroxy - 3 - naphthoate) in 10 parts of water. The mixture is stirred and filtered. The solid residue is washed with water, dried and crystallised from a mixture of 10 parts of ethyl acetate and 20 parts of ether. There is thus obtained di - [1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol] 1,1' - methylene - bis - (2 - hydroxy - 3 - naphthoate), m.p. 186—188°C.

EXAMPLE 21

To a solution of 1 part of 1 - isopropyl - amino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride in 10 parts of water there is added a suspension of 10 parts of a sulphonated polystyrene resin ["Zeo-Karb" 225(SCR 9)—"Zeo-Karb" is a Trade Mark] in 40 parts of water. The mixture is stirred for 1 hour at ambient temperature. It is then filtered and the solid residue is washed with water. There is thus obtained a complex salt of 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol with a sulphonated polystyrene resin which has a base content of 13.5%.

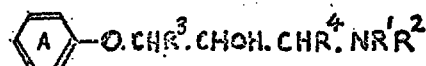
WHAT WE CLAIM IS:—

1. Racemic alkanolamine derivatives of the formula:—



wherein R¹ stands for hydrogen R² stands for an alkyl radical or not more than 10 carbon atoms which is branched at the α -carbon atom, or for the 2 - hydroxy - 1,1 - dimethyl - ethyl or 1 - methyl - 3 - phenylpropyl radical, R³ and R⁴, which may be the same or different, stand for hydrogen or for alkyl radicals of not more than 5 carbon atoms, and the benzene ring (A) bears a single substituent in the 3- and 4- position only which is a halogen atom, an alkyl radical containing not more than 4 carbon atoms, an alkoxy, alkylthio, alkanoyl, aralkanoyl, aroyl, aryl, aryloxy, alkylaryloxy, arylthio, arylsulphonyl, aryl-amino, aralkyl, aralkoxy or alkenyl radical each containing not more than 10 carbon atoms, a halogenoalkyl radical containing not more than 5 carbon atoms, or a hydroxy or nitro radical, or the benzene ring (A) bears a single substituent in the 2- position only which is a hydroxy, nitro or iodo substituent or an alkanoyl, aralkanoyl, aroyl, aryl, aryloxy, alkylaryloxy, arylthio, arylsulphonyl, aryl-amino, aralkyl or aralkoxy substituent each containing not more than 10 carbon atoms, or the benzene ring (A) bears two, three or four substituents which are selected from the values defined above for the single substituent in the 3- or 4- position only, provided that the 2- and 6- positions of the benzene ring (A) are not both substituted; and the carboxylic esters thereof; and the salts thereof.

2. Racemic alkanolamine derivatives of the formula:—



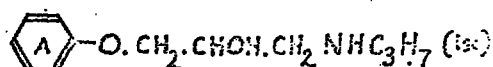
wherein R¹ stands for hydrogen; wherein R² stands for an alkyl radical of not more than 10 carbon atoms which is branched at the α -carbon atom, or for the 2 - hydroxy - 1,1 - dimethylethyl or 1 - methyl - 3 - phenyl -





propyl radical wherein R^3 and R^4 , which may be the same or different, stand for hydrogen or for alkyl radicals of not more than 5 carbon atoms; and wherein the benzene ring (A) bears a single substituent in the 3- or 4-position only which is a halogen atom, a hydroxy or nitro radical, a halogenoalkyl radical containing not more than 5 carbon atoms, alkyl radical containing not more than 4 carbon atoms, or an alkoxy, alkanoyl, aralkanoyl, aroyl, aryl, aryloxy, arylthio, arylsulphonyl, aralkyl, or alkenyl radical each containing not more than 10 carbon atoms, or the benzene ring (A) bears a single substituent in the 2-position only which is a hydroxy radical or an alkanoyl, aralkanoyl, aroyl, aryl, aryloxy, arylthio, arylsulphonyl or aralkyl radical each containing not more than 10 carbon atoms, or the benzene ring (A) bears two, three or four substituents which are selected from the values defined above for the single substituent in the 3- or 4- position only provided that the 2- and 6- positions of the benzene ring (A) are not both substituted and the salts thereof.

3. Racemic alkanolamine derivatives of the formula:—



wherein the benzene ring (A) bears a single substituent in the 3- or 4- position only which is a halogen atom, an alkyl, alkoxy or alkanoyl radical each containing not more than 4 carbon atoms, an aralkyl radical of not more than 10 carbon atoms, or a hydroxy or nitro radical, or wherein the benzene ring (A) bears a single substituent in the 2-position only which is a hydroxy radical or an alkanoyl radical of not more than 4 carbon atoms or an aralkyl radical of not more than 10 carbon atoms, or wherein the benzene ring (A) bears two or three substituents which are selected from halogen atoms, alkyl, alkoxy and alkanoyl radicals each containing not more than 4 carbon atoms, aralkyl radicals of not more than 10 carbon atoms and hydroxy and nitro radicals, provided that the 2- and 6- positions of the benzene ring (A) are not both substituted, and the salts thereof.

4. Alkanolamine derivatives as claimed in claim 1 or 2 wherein R^3 stands for the isopropyl, s-butyl or t-butyl, radical.

5. Alkanolamine derivatives as claimed in any of claims 1, 2 and 4 wherein R^3 or R^4 stands for the methyl radical.

6. Alkanolamine derivatives as claimed in any of claims 1, 4 and 5 wherein the benzene ring (A) bears one or more substituents selected from fluorine, chlorine, bromine and iodine atoms and methyl, ethyl, isopropyl, t-butyl, methoxy, ethoxy, n-butoxy, methylthio, acetyl, benzoyl, hydroxy, trifluoromethyl, phenyl, phenoxy, 4-tolyloxy, phenylthio, phenylsul-

phenyl, anilino, benzyl, α, α -dimethylbenzyl benzyloxy and nitro radicals.

7. Alkanolamine derivatives as claimed in any of claims 2 to 5 wherein the benzene ring (A) bears one or more substituents selected from fluorine, chlorine and bromine atoms and methyl, ethyl, isopropyl, t-butyl, methoxy, ethoxy, n-butoxy, acetyl, benzoyl, hydroxy, trifluoromethyl, phenyl, phenoxy, phenylthio, phenylsulphonyl, benzyl and nitro radicals.

8. Racemic 1 - (3 - tolyloxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

9. Racemic 1 - (4 - tolyloxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

10. Racemic 1 - (2,3 - dimethylphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

11. Racemic 1 - (2,4 - dimethylphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

12. Racemic 1 - (3,4 - dimethylphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

13. Racemic 1 - (3,5 - dimethylphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

14. Racemic 1 - (3 - ethyl - 5 - methyl - phenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

15. Racemic 1 - (3 - chlorophenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

16. Racemic 1 - (2,3 - dichlorophenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

17. Racemic 1 - (3,5 - dichlorophenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

18. Racemic 1 - (3 - fluorophenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

19. Racemic 1 - (4 - chloro - 3 - methyl - phenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

20. Racemic 1 - (3 - methoxyphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

21. Racemic 1 - (2 - hydroxyphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

22. Racemic 1 - (3 - nitrophenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

23. Racemic 1 - (3 - trifluoromethyl - phenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

24. Racemic 1 - (2 - phenylphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

25. Racemic 1 - (2 - phenoxyphenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

26. Racemic 1 - (2 - benzoyl - 5 - methoxy-



phenoxy) - 3 - isopropylamino - 2 - propanol, and the salts thereof.

27. Racemic 1 - (2,3 - dichlorophenoxy) - 3 - s - butylamino - 2 - propanol, and the salts thereof.

28. Racemic 1 - (2 - hydroxy - 1,1 - di - methylethylamino) - 3 - (3 - tolyloxy) - 2 - propanol, and the salts thereof.

29. Racemic 1 - t - butylamino - 3 - (3 - tolyloxy) - 2 - propanol and the salts thereof.

30. Racemic 1 - (2,4,5 - trichlorophenoxy) - 3 - isopropylamino - 2 - propanol and the salts thereof.

31. Racemic 1 - (3 - phenoxyphenoxy) - 3 - isopropylamino - 2 - propanol and the salts thereof.

32. Racemic 1 - (4 - anilinophenoxy) - 3 - isopropylamino - 2 - propanol and the salts thereof.

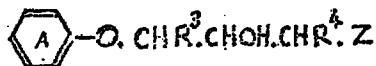
33. Racemic [2 - (4 - tolyloxy)phenoxy] - 3 - isopropylamino - 2 - propanol and the salts thereof.

34. Racemic 1 - (3,5 - dimethylphenoxy) - 3 - (1 - methyl - 3 - phenylpropylamino) - 2 - propanol, and the salts thereof.

35. Carboxylic esters as claimed in any of claims 1 and 4 to 6 which are O-esters derived from a saturated or unsaturated aliphatic carboxylic 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 of not more than 15 carbon atoms, for example benzoic acid, and the salts thereof.

36. Salts as claimed in any of claims 1 to 35 which are acid-addition salts derived from an inorganic acid, for example hydrochlorides, hydrobromides, phosphates or sulphates, or derived from an organic acid, for example oxalates, lactates, tartrates, acetates, salicylates, citrates, benzoates, β -naphthoates, adipates or 1,1' - methylene - bis - (2 - hydroxy - 3 - naphthoates), or derived from an acidic synthetic resin, for example a sulphonated polystyrene resin.

37. A process for the manufacture of the alkanolamine derivatives claimed in any of claims 1 to 34 and 36 which comprises the interaction of a halogeno compound of the formula:—



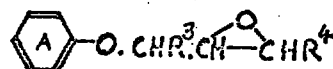
wherein Z stands for a chlorine, bromine or iodine atom, and R^3 , R^4 and A have the meanings stated in claim 1, with an amine of the formula NHR^1R^2 , wherein R^1 and R^2 have the meanings stated in claim 1.

38. A process as claimed in claim 37 wherein Z stands for the chlorine or bromine atom.

39. A process as claimed in claim 37 or 38 wherein the interaction is accelerated or completed by the application of heat.

40. A process as claimed in any of claims 37 to 39 which is carried out in an inert diluent or solvent.

41. A process for the manufacture of the alkanolamine derivatives claimed in any of claims 1 to 34 and 36 which comprises the interaction of an epoxide of the formula:—

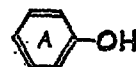


wherein R^3 , R^4 and A have the meanings stated in claim 1, with an amine of the formula NHR^1R^2 , wherein R^1 and R^2 have the meanings stated in claim 1.

42. A process as claimed in claim 41 which is accelerated or completed by the application of heat.

43. A process as claimed in claim 41 or 42 which is carried out in an inert diluent or solvent, for example ethanol.

44. A process for the manufacture of the alkanolamine derivatives claimed in any of claims 1 to 34 and 36 which comprises the interaction of a compound of the formula:—



wherein A has the meaning stated in claim 1, with a compound of the formula:—

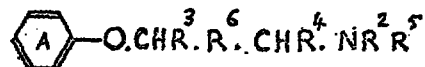


wherein R^1 , R^2 , R^3 and R^4 have the meanings stated in claim 1, and Z has the meaning stated in claim 37.

45. A process as claimed in claim 44 which is carried out in the presence of an acid-binding agent.

46. A process as claimed in claim 44 wherein an alkali metal derivative of the phenol reactant, for example the sodium or potassium derivative, is used as starting material.

47. A process for the manufacture of the alkanolamine derivatives claimed in any of claims 1 to 34 and 36 which comprises the hydrogenolysis of a compound of the formula:—



wherein R^3 , R^4 and A have the meanings stated in claim 1, R^6 stands for a hydrogenolysable radical and R^5 stands for the carbonyl radical (CO).

48. A process as claimed in claim 47 wherein R^5 stands for the benzyl radical.



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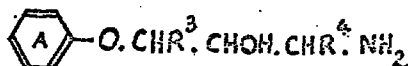
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49. A process as claimed in claim 47 or 48 wherein the hydrogenolysis is effected by catalytic hydrogenation, for example hydrogenation in the presence of a palladium-on-charcoal catalyst, in an inert diluent or solvent, for example ethanol.

50. A process for the manufacture of those of the alkanolamine derivatives claimed in any of claims 1 to 27, 30 to 34 and 36 wherein R^2 stands for a radical of the formula $—CHR^8R^9$, wherein R^8 stands for an alkyl radical of not more than 8 carbon atoms and R^9 stands for an alkyl radical of not more than 8 carbon atoms, or R^8 stands for the methyl radical and R^9 stands for the β -phenylethyl radical, which comprises the interaction of an amino derivative of the formula:—



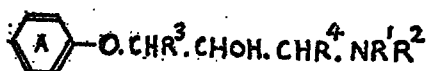
wherein R^3 , R^4 and A have the meanings stated in claim 1, with a carbonyl compound of the formula $R^8.CO.R^9$ wherein R^8 and R^9 have the meanings stated above, under reducing conditions.

51. A process as claimed in claim 50 wherein the reducing conditions are provided by the presence of hydrogen and a hydrogenation catalyst, for example platinum, in an inert diluent or solvent, for example ethanol, and/or, an excess of the carbonyl compound used as starting material.

52. A process as claimed in claim 50 wherein the reducing conditions are provided by the presence of an alkali metal borohydride, for example sodium borohydride, in an inert diluent or solvent, for example aqueous methanol, and/or in an excess of the carbonyl compound used as starting material.

53. A process as claimed in claims 50 to 52 wherein the amino derivative used as starting material is generated *in situ*, for example by the reduction of the corresponding α -diazo-ketone, α -azidoketone, α -hydroxyiminoketone, α -nitroketone, α -nitro-alcohol, cyanhydrin or acyl cyanide.

54. A process for the manufacture of those of the alkanolamine derivatives claimed in any of claims 1 to 7, 21 and 36 wherein the benzene ring (A) bears a hydroxy substituent, and optionally may bear one or more further substituents selected from those stated in claim 1, which comprises the hydrogenolysis of a compound of the formula:—



wherein R^1 , R^2 , R^3 and R^4 have the meanings stated in claim 1, and wherein the benzene ring (A) bears a substituent of the formula $—OR^7$, wherein R^7 stands for a hydrogenolysable radical and wherein the benzene ring (A) may optionally be further substituted as stated above.

55. A process as claimed in claim 54 wherein R^7 stands for the benzyl radical.

56. A process as claimed in claim 54 or 55 which is effected by catalytic hydrogenation, for example in the presence of a palladium-on-carbon catalyst, in an inert diluent or solvent, for example ethanol.

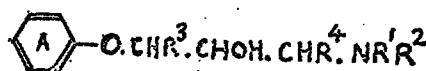
57. A process for the manufacture of the alkanolamine carboxylic esters claimed in any of claims 1, 4 to 6 and 35 which comprises the interaction of the corresponding alkanolamine derivatives or salt thereof with an acylating agent.

58. A process as claimed in claim 57 in which the acylating agent is an acid halide or anhydride derived from a saturated or unsaturated aliphatic carboxylic acid or from an aromatic carboxylic acid, for example acetic anhydride or benzoyl chloride.

59. A process as claimed in claim 57 or 58 which is carried out in a diluent or solvent.

60. A process as claimed in claim 59 in which the acylating agent is an acid anhydride and the diluent or solvent is the acid from which the anhydride is derived.

61. A process for the manufacture of those of the alkanolamine derivatives claimed in any of claims 1, 2, 4 to 7 and 36 wherein the benzene ring (A) bears an arylsulphonyl substituent, which comprises the oxidation of a compound of the formula:—



wherein R^1 , R^2 , R^3 and R^4 have the meanings stated in claim 1 and wherein the benzene ring (A) bears an arylthio substituent.

62. A process as claimed in claim 61 wherein the oxidizing agent is hydrogen peroxide.

63. Alkanolamine derivatives, claimed in any of claims 1 to 36, as described in the foregoing Examples 1 to 21.

64. Process for the manufacture of alkanolamine derivatives, claimed in any of claims 1 to 36, substantially as described in the foregoing Examples 1 to 21.

WALTER SCOTT,
Agent for the Applicants.