

PATENT SPECIFICATION

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 62X 630 634 650 652 65X 660 661 662 668
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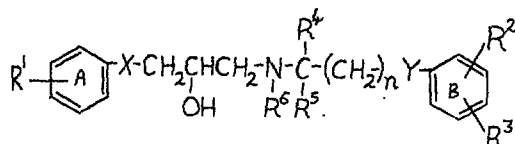
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(54) PROPANOLAMINE DERIVATIVES

(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, 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:—

The invention relates to novel propanolamine derivatives, which have useful therapeutic properties, and is particularly concerned with 1-phenoxy-3-phenylalkyl-amino-2-propanols and 1-phenoxy-3-phenoxyalkylamino-2-propanols, and analogous 1-phenyl-thio, 3-phenyl-thio-alkylamino-, 3-phenyl-sulphinyl-alkylamino-, 3-phenyl-sulphonyl-alkylamino- and 3-phenylamino-alkylamino-2-propanols, in which the phenyl group of the 3-substituent carries an electron-withdrawing polar substituent, and analogous compounds in which one or other of the phenyl groups is replaced by a naphthyl group.

The compounds of the invention are those having the general formula:



where: R^1 represents hydrogen, halogen, or a lower alkyl, phenyl, lower alkoxy or phenyl-substituted lower alkyl group;

R^2 represents hydrogen, or up to 2 halogen, lower alkyl or lower alkoxy substituents;

R^3 represents an electron-withdrawing polar substituent;

R^4 and R^5 each represent hydrogen or a lower alkyl group;

R^6 represents hydrogen or a lower alkyl, lower alkanoyl or benzyl group; either of the benzene rings A and B may be optionally substituted further by a $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ radical to form a naphthyl group;

X represents oxygen or sulphur;

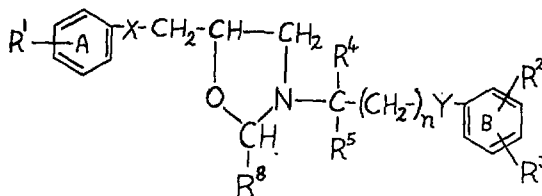
and either Y represents oxygen, sulphur, or a sulphinyl, sulphonyl or imino group and n is 1, 2 or 3;

or Y represents a direct link and n is 0, 1, 2, 3 or 4;

the carboxylic acid esters and aldehyde condensation products of such compounds, and their pharmaceutically acceptable acid addition salts.

In this specification "halogen" comprises fluorine, chlorine, bromine and iodine; "imino group" indicates the group $-\text{N}(\text{R}')-$, where R' represents hydrogen or a lower alkyl group; and the term "lower", used to qualify an alkyl, alkoxy or alkanoyl group, indicates that such group contains up to 4 carbon atoms.

The aldehyde condensation products of the compounds of the invention are oxazolidines, having the formula:



which are formed by condensation of compounds of the invention in which R^8 is hydrogen with an aldehyde of the formula R^8CHO , where R^8 is hydrogen or a lower alkyl group.

One preferred class of compounds consists of those in which R^4 is hydrogen or a methyl group, R^5 is hydrogen, Y is oxygen and n is 1. Another preferred class consists of those in which R^2 is hydrogen, methyl, methoxy, dimethoxy or chloro and R^3 is a carbamoyl group, Y is oxygen and n is 1. Particularly preferred are those compounds in which R^3 is an unsubstituted carbamoyl group in the 2- position or the 4- position on the phenyl group, and when such group is in the 2- position then R^2 is a methyl or methoxy group in the 4-, 5- or 6- position on the phenyl group.

The compounds of the invention have the property of blocking the β -adrenergic receptors and are useful in the curative or prophylactic treatment of cardiac conditions, such as angina pectoris and cardiac arrhythmias, and in the treatment of hypertension.

Electron-withdrawn polar substituents are those which contain a polar group with its electropositive atom adjacent to the phenyl ring, including those in which the polar group is separated from the phenyl ring by a methylene or ethylene group. Polar groups include the carbonyl, sulphonyl, sulphinyl, cyano, azido, nitro and trihalomethyl groups, and R^3 in the above formula may therefore be, for example, a carboxy, lower alkoxycarbonyl, formyl, lower alkanoyl, carbamoyl, sulpho, sulphino, alkoxysulphonyl, alkoxysulphinyl, sulphamoyl, cyano, azido, nitro or trifluoromethyl group, or any such group separated from the phenyl ring by a methylene or ethylene group, e.g. a carboxymethyl, lower-alkoxycarbonyl-methyl, formyl-methyl, acetonyl and other lower-alkanoyl-methyl radicals, carbamoyl-methyl, sulphomethyl, sulphinomethyl, lower-alkoxysulphonyl (and sulphinyl)-methyl, sulphamoyl-methyl and cyanomethyl, as well as the corresponding polar-substituted ethyl radicals.

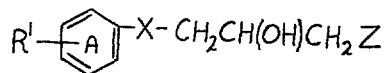
Carbamoyl and sulphamoyl groups are those having the formula $-\text{CO.NR}^9\text{R}^{10}$ and $-\text{SO}_2.\text{NR}^9\text{R}^{10}$, respectively, where R^9 and R^{10} are each hydrogen or a lower alkyl or an aryl group or together with the nitrogen atom to which they are attached form a heterocyclic group, e.g. a pyrrolidino, piperidino, piperazino or morpholino group, and N-amino derivatives of those in which R^9 is hydrogen, e.g. the $-\text{CO.NHNH}_2$ group and alkyl or aryl derivatives thereof.

Acids from which pharmaceutically acceptable addition salts of the compounds of the invention can be prepared are those which form non-toxic addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, saccharate and *p*-toluene sulphonate salts.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier or vehicle selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

The compounds of the invention may be prepared in a number of ways:

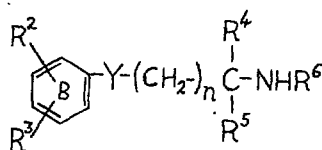
(1) A compound of the formula:



5

where Z is halogen or any other suitable "leaving" group, e.g. a sulphonyloxy group such as $\text{C}_6\text{H}_5\text{SO}_2\text{O}-$ or $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{O}-$, may be reacted with an amine of the formula:

5



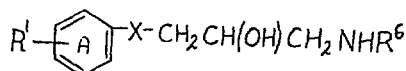
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where R^6 is hydrogen, lower alkyl or benzyl, preferably by heating, either in the presence of excess amine and a suitable solvent, e.g. methanol, or in equimolar proportions in the presence of an alkali such as sodium bicarbonate. After filtration and evaporation to dryness the product is recovered by distillation *in vacuo* or by dissolving in a suitable solvent and precipitating as a suitable salt, e.g. the hydrochloride, maleate, fumarate or oxalate, by addition of the appropriate acid.

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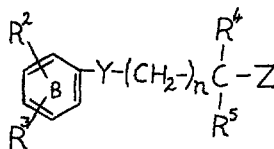
(2) An amine of the formula:

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where R^6 is hydrogen, lower alkyl or benzyl, may be reacted with a compound of the formula:

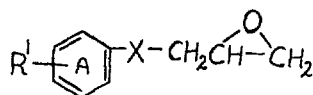


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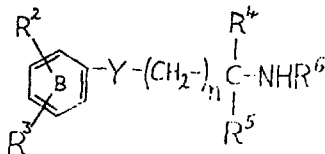
and the product recovered, the conditions for reaction and recovery being similar to those given for method (1).

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(3) An epoxy compound of the formula:



may be reacted with an amine of the formula:

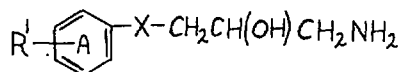


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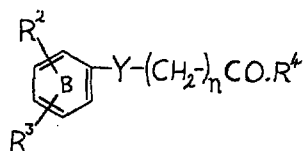
where R^6 is hydrogen, lower alkyl or benzyl, preferably in equimolar proportions at ambient temperature, and the product recovered as in methods (1) and (2).

25

(4) An amine of the formula:



may be reacted with an aldehyde or ketone of the formula:



5 to give the corresponding Schiff's base, which is reduced with hydrogen in the presence of a hydrogenation catalyst, e.g. platinum, or with sodium borohydride, to a compound of the invention in which R^5 and R^6 are each hydrogen. This is the preferred method for the preparation of compounds in which R^4 is lower alkyl. 5

10 The aldehyde condensation products of the compounds of the invention may be prepared by reacting a compound of the invention in which R^6 is hydrogen with an aldehyde of the formula $R^8\text{CHO}$, where R^8 is hydrogen or lower alkyl, in a diluent or solvent, e.g. ethanol, preferably in the presence of an acid catalyst, e.g. hydrochloric or acetic acid, and preferably at an elevated temperature. The water formed in the reaction may be removed by azeotropic distillation by means of an entraining solvent, e.g. benzene, or by a dehydrating agent such as anhydrous potassium carbonate. 15

15 Esters of compounds of the invention, and compounds in which R^6 is lower alkyl, may be formed by acylation of the free hydroxyl group or the secondary amine group, respectively, in a conventional manner with a carboxylic acid chloride or anhydride derived from a saturated aliphatic acid or, in the case of esters only, from an unsaturated aliphatic acid or from an aromatic acid, e.g. acetic anhydride or benzoyl chloride. 20

The invention is illustrated by the following Examples in which temperatures are given as $^{\circ}\text{C}$.

EXAMPLE 1

25 2-(2-Bromoethoxy)benzamide (12.2g.), DL-1-amino-3-(2-methylphenoxy)propan-2-ol (9 g.), sodium bicarbonate (4.2 g.) and ethanol (100 ml.) were refluxed together for 16 hr. The mixture was cooled, filtered and evaporated *in vacuo* to give a semi-solid residue. The residue was stirred with benzene (60 ml.) and the insoluble material was removed by filtration. Evaporation of the benzene liquors gave a gum which was re-dissolved in ethanol and converted to an oxalate by treatment with ethereal oxalic acid solution. The oxalate was recrystallised from aqueous ethanol as white needles m.p. 121°C . Basification of the oxalate gave the free base of DL-1-[2-(2-carbamoylphenoxy)ethylamino]-3-(2-methylphenoxy)propan-2-ol (2 g.) as a white solid, m.p. $105.5-106^{\circ}\text{C}$. 30

35 *Analysis* found: C, 66.4; H, 6.9; N, 8.0%
Calc'd for: $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4$: C, 66.25; H, 7.0; N, 8.1% 35

EXAMPLE 2

40 2-(3-Chloropropoxy)benzamide (19.4 g.), DL-1-amino-3-(2-methylphenoxy)propan-2-ol (16.4 g.), sodium bicarbonate (11.4 g.) and ethanol (200 ml.) were refluxed together for 16 hr. The mixture was cooled and filtered to remove inorganic material. The ethanolic liquors were evaporated *in vacuo* to give the crude product as a sticky solid (35.5 g.). Recrystallisation from ethanol gave two crops which differed in physical properties. The second crop (10.3 g.) was recrystallised from isopropanol to give DL-1-[3-(2-carbamoylphenoxy)propylamino]-3-(2-methylphenoxy)propan-2-ol as a white crystalline solid (8 g.) m.p. $117-118^{\circ}\text{C}$. 45

Analysis — found: C, 66.95; H, 7.5; N, 7.7%
Calc'd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4$: C, 67.0; H, 7.3; N, 7.8%

EXAMPLE 3

A mixture of 2-carbamoyl-phenoxy-acetone (19g.) DL-1-amino-3-(2-methylphenoxy)propan-2-ol (18.1g.) and ethanol (250ml.) was treated with platinum oxide (100mg.) and hydrogenated at a pressure of 60 p.s.i. and 50°C. for 12 hours. The catalyst was removed by filtration followed by evaporation to dryness *in vacuo*. The oily residue was converted to the oxalate and dissolved in a boiling mixture of ethanol and water. On cooling, the oxalate of unchanged starting material was deposited and removed by filtration. The ethanolic liquors were evaporated to dryness and basified with sodium carbonate to give DL-1-[2-(2-carbamoyl phenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol as the free base, which after extraction into chloroform, followed by drying and evaporation, was obtained as an oily solid. Recrystallisation from ethyl acetate gave the product as a white solid (2g.) m.p. 131—4°C.

Analysis — found: C, 67.4; H, 7.55; N, 7.6%
Calc'd for $H_{20}H_{26}N_2O_4$: C, 67.0; H, 7.3; N, 7.8%

EXAMPLE 4

1-(2-Methylphenoxy)-2:3-epoxypropane (6g.) and N-(4-ethoxycarbonylphenyl) ethylene diamine (5g.) were heated together in ethanol (20ml.) for 2 hrs., followed by standing at room temperature for 16hrs. The ethanol was evaporated *in vacuo* and the residue was dissolved in ether. The oxalate was precipitated by the addition of ethereal oxalic acid and after two recrystallisations (ethanol-water) DL-N-(4-ethoxycarbonylphenyl)-N'-[3-(2-methylphenoxy)-2-hydroxypropyl]ethylenediamine oxalate was obtained as a white crystalline solid (2.2 g.) m.p. 161.5—162.5°C.

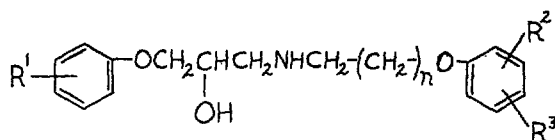
Analysis — found: C, 59.9 H, 6.5; N, 6.0
Calc'd for $C_{23}H_{30}N_2O_8$: C, 59.7; H, 6.5; N, 6.1%

EXAMPLE 5

1-(4-Dimethylsulphamoylphenoxy)-2-bromethane (6 g.), DL-3-(2-methylphenoxy)-1-aminopropan-2-ol (5 g.) and sodium bicarbonate (1.6 g.) were refluxed together in absolute ethanol (100 ml.) for 16 hr. After cooling the mixture was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in ether and converted to the oxalate by treatment with ethereal oxalic acid solution. The oxalate was recrystallised from water and DL-1-[2-(4-dimethylsulphamoylphenoxy)ethylamino]-3-(2-methylphenoxy)propan-2-ol oxalate was obtained as a white crystalline solid (1.6 g.) m.p. 182—183.5°C.

Analysis — found: C, 52.3; H, 5.9; N, 5.75; S, 6.5%
Calc'd for $C_{22}H_{30}N_2O_6S$: C, 53.0; H, 6.1; N, 5.6; S, 6.4%

The following compounds were prepared by the methods of Examples 1 or 2, from the appropriate (halo-alkoxy) benzene derivative and DL-1-amino-3-phenoxypropan-2-ol derivative, as indicated:



Example	R ¹	R ²	R ³	n	(halo-alkoxy) benzene)
6	2-CH ₃	H	2-NO ₂	1	1-(2-bromoethoxy)-2-nitrobenzene
7	2-CH ₃	H	4-CONH ₂	1	4-(2-bromoethoxy)-benzamide
8	2-CH ₃	4-CH ₃	2-CONH ₂	1	2-(2-bromoethoxy)-5-methylbenzamide
9	2-CH ₃	3-OCH ₃	4-CONH ₂	1	4-(2-bromoethoxy)-2-methoxybenzamide
10	2-CH ₃	2-CH ₃	4-CONH ₂	1	4-(2-bromoethoxy)-3-methylbenzamide
11	2-CH ₃	H	4-CH ₂ CONH ₂	1	4-(2-bromoethoxy)phenylacetamide
12	2-CH ₃	4-OCH ₃	2-CONH ₂	1	2-(2-bromoethoxy)-4-methoxybenzamide
13	2-CH ₃	3-CH ₃	4-CONH ₂	1	4-(2-bromoethoxy)-3-methylbenzamide
14	2-Cl	H	4-CONH ₂	1	4-(2-bromoethoxy) benzamide
15	2-CH ₃	H	4-CONH-Ph	1	4-(2-bromoethoxy)-N-phenylbenzamide
16	2-CH ₃	H	4-CONH ₂	2	4-(3-chloropropoxy)benzamide
17	2-CH ₃	H	3-CONH ₂	1	3-(2-bromoethoxy) benzamide
18	2-CH ₃	2,6-di-OCH ₃	4-CONH ₂	1	4-(2-bromoethoxy)-2,6-dimethoxy-benzamide
19	2-CH ₃	H	2-CONHCH ₃	1	2-(2-bromoethoxy)-N-methylbenzamide
20	2-CH ₃	H	4-CON(CH ₃) ₂	1	4-(2-bromoethoxy)-N,N-dimethylbenzamide
21	2-CH ₃	H	4-CONHCH ₃	1	4-(2-bromoethoxy)-N-methylbenzamide

The products, isolated as the free base in each case unless otherwise stated, were characterised as follows, calculated analytical figures being given in brackets below the found values in each case:

Example	m.pt.	Analysis %		
		C	H	N
6	100—102°	62.38 (62.41)	6.35 6.46	7.92 8.09)
7	157—159°	66.2 (66.25)	7.0 7.0	7.8 8.1)
8	103—104°	66.7 (67.0)	7.3 7.3	7.8 7.8)
9	187—190° (oxalate)	57.1 (56.9)	6.3 6.1	6.2 6.0)
10	178—181° (oxalate)	58.9 (58.9)	6.6 6.3	6.5 6.3)
11	129—130°	66.7 (67.0)	7.4 7.3	7.7 7.8)
12	108—110°	64.0 (64.2)	6.6 7.0	7.4 7.5)
13	115—118°	66.9 (67.0)	7.1 7.3	7.9 7.8)
14	234—238° (hydrochloride)	54.2 (53.9)	5.6 5.5	7.1 7.0)
15	138—9°	71.1 (71.4)	6.7 6.7	6.5 6.7)
16	118—119°	66.7 (67.0)	7.2 7.3	7.6 7.8)
17	191—195° (hydrochloride)	59.8 (59.9)	6.4 6.6	6.9 7.4)
18	155—156°	62.0 (62.4)	6.9 7.0	6.6 6.9)
19	96—98°	67.1 (67.0)	7.4 7.3	7.7 7.8)
20	124—127° (oxalate)	59.9 (59.7)	6.7 6.5	5.8 6.1)
21	181—184° (oxalate)	58.3 (58.9)	6.4 6.3	6.1 6.3)

EXAMPLE 22

1-[2-(2-Carbamoyl-4-methylphenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol

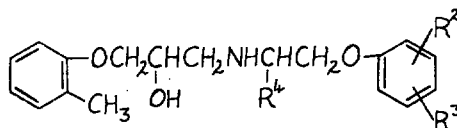
- 5 2-Carbamoyl-4-methylphenoxyacetone (5g.) and DL-1-amino-3-(2-methylphenoxy)propan-2-ol (4g.) were refluxed in ethanol for 1 hour. The ethanol was removed *in vacuo* and replaced with methanol (50 ml.) followed by the slow addition of sodium borohydride (2g.) at 25—30°. The mixture was stirred for 30 minutes and then poured onto ice and acidified with acetic acid. Re-basification with sodium carbonate was followed by extraction with chloroform. The extract was dried over magnesium sulphate
10 and evaporated *in vacuo* to give an oil which solidified on standing. Recrystallisation from a mixture of ethanol and water gave the pure free base (3.5g.) m.p. 110.5—113°.

Analysis: Found — C, 67.23; H, 7.36; N, 6.99%

C, 66.65; H, 7.16; N, 7.21%

Calc'd for: $C_{21}H_{28}N_2O_4$ — C, 67.72; H, 7.58; N, 7.52%

- 15 The following compounds were prepared by the method of Example 22, from DL-1-amino-3-(2-methylphenoxy)propan-2-ol and the appropriate ketone, as indicated:



Example	R ²	R ³	R ⁴	Ketone
23	4-Cl	2-CONH ₂	CH ₃	2-carbamoyl-4-chlorophenoxyacetone
24	H	4-CONH ₂	CH ₃	4-carbamoylphenoxyacetone
25	5-CH ₃	2-CONH ₂	CH ₃	2-carbamoyl-5-methylphenoxyacetone
26	H	3-CONH ₂	CH ₃	3-carbamoylphenoxyacetone
27	H	3-CON(CH ₃) ₂	CH ₃	3-dimethylcarbamoylphenoxyacetone
28	H	2-CONH ₂	C ₂ H ₅	1-(2-carbamoylphenoxy)butan-2-one
29	H	4-NO ₂	CH ₃	4-nitrophenoxyacetone
30	H	4-COOCH ₃	CH ₃	4-methoxycarbonylphenoxyacetone
31	H	4-CN	CH ₃	4-cyanophenoxyacetone
32	H	3-CF ₃	CH ₃	3-trifluoromethylphenoxyacetone
33	H	4-CH ₂ CONH ₂	CH ₃	4-carbamoylmethylphenoxyacetone
34	H	2-CH ₂ CONH ₂	CH ₃	2-carbamoylmethylphenoxyacetone
35	H	2-CONHC ₆ H ₅	CH ₃	2-(N-phenylcarbamoyl)phenoxyacetone
36	2-OCH ₃	5-CONH ₂	CH ₃	5-carbamoyl-2-methoxyphenoxyacetone

Example	R ²	R ³	R ⁴	Ketone
37	4-CH ₃	2-CON(CH ₃) ₂	CH ₃	2-(N,N-dimethylcarbamoyl)-4-methylphenoxy-acetone
38	3-CH ₃	4-CONH ₂	CH ₃	4-carbamoyl-3-methyl-phenoxyacetone
39	H	4-SO ₂ NH ₂	CH ₃	4-sulphamoyl-phenoxyacetone
40	2-OCH ₃	4-CONH ₂	CH ₃	4-carbamoyl-2-methoxyphenoxyacetone
41	4-OCH ₃	2-CONH ₂	CH ₃	2-carbamoyl-4-methoxyphenoxyacetone
42	2-CH ₃	4-CONH ₂	CH ₃	4-carbamoyl-2-methylphenoxyacetone
43	3-CH ₃	4-NO ₂	CH ₃	3-methyl-4-nitrophenoxyacetone
44	2-CH ₃	5-CONH ₂	CH ₃	5-carbamoyl-2-methylphenoxyacetone
45	6-CH ₃	2-CONH ₂	CH ₃	2-carbamoyl-6-methylphenoxyacetone
46	2,6-di-CH ₃	4-COOCH ₃	CH ₃	4-methoxycarbonyl-2,6-dimethylphenoxyacetone
47	5-CH ₃	3-CONH ₂	CH ₃	3-carbamoyl-5-methyl-phenoxyacetone
48	3-OCH ₃	4-CONH ₂	CH ₃	4-carbamoyl-3-methoxyphenoxyacetone
49	2,6-di-OCH ₃	4-CONH ₂	CH ₃	4-carbamoyl-2,6-dimethoxyphenoxyacetone

The products, isolated as the free base in each case unless otherwise stated, were characterised as follows, calculated analytical figures being shown as before:

Example	m.pt.	Analysis, %		
		C	H	N
23 (1)*	132—134°	61.21	6.50	6.84
(2)*	119—121°	61.05 (61.15)	6.33 6.41	6.85 7.13)
24	113—114.5°	66.44 (67.02)	7.11 7.31	7.49 7.82)
25	138°	67.88 (67.72)	7.08 7.58	6.80 7.52)
26	116—117°	65.74 (65.74)	7.52 7.54	7.22 7.48)†
27	73—75°	67.97 (68.36)	7.57 7.82	7.01 7.25)
28	128—129°	67.35 (67.72)	7.18 7.58	7.19 7.52)
29	89.5°	62.99 (63.32)	6.80 6.71	7.44 7.77)
30	75—76	67.39 (67.54)	7.48 7.29	3.93 3.75)
31	74—75°	70.29 (70.56)	6.80 7.11	8.17 8.23)
32	75—76°	62.94 (62.61)	6.19 6.3	3.28 3.65)
33	145—6°	68.0 (67.7)	7.40 7.58	7.26 7.52)
34	136—138°	67.5 (67.7)	7.3 7.6	7.3 7.5)
35	176—178° (hemi-fumarate)	68.3 (68.3)	6.7 6.6	5.6 5.7)
36	100—105°	64.5 (64.9)	7.4 7.3	6.9 7.2)
37	(Oil) —	69.1 (69.0)	8.0 8.1	6.5 7.0)
38	126—129°	67.3 (67.7)	7.4 7.6	7.1 7.5)

* Racemic pairs of diastereoisomers.

† This product contains $\frac{1}{2}$ mol. of occluded methanol

Example	m.pt.	Analysis %		
		C	H	N
39	185—186° (hemi-fumarate)	55.6 (55.8)	6.2 6.2	5.9 6.2)
40	132—142°	65.0 (64.9)	7.1 7.3	7.0 7.2)
41	109—110°	64.7 (64.9)	7.1 7.3	7.0 7.2)
42	110—113°	67.7 (67.7)	7.6 7.6	7.3 7.5)
43	76—77°	64.4 (64.2)	7.1 7.0	7.5 7.5)
44	122—123°	67.2 (67.7)	7.1 7.6	7.1 7.5)
45	170—171.5° (oxalate)	63.3 (63.3)	7.0 7.0	7.0 6.7)
46	128—130° (hydrochloride)	63.3 (63.1)	7.6 7.4	3.2 3.2)
47	(oil) —	(identified by spectroscopic evidence only)		
48	134—143° (hydrochloride)	(— ditto —)		
49	114—126° (hydrochloride)	(— ditto —)		

EXAMPLE 50

1-[2-(4-N-Aminocarbamoyl-phenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol.

5 This compound was prepared from the product of Example 30 by heating with hydrazine hydrate in ethanol. m.p. 129° 5

Analysis: Found — C, 64.2; H, 7.1; N, 11.2%
Calc'd for $C_{20}H_{27}N_3O_4$ — C, 64.3; H, 7.3; N, 11.3%

EXAMPLE 51

10 1-[2-(4-Carbamoyl-phenoxy)-1-methyl-ethylamino]-3-(1-naphthoxy)propan-2-ol. 10

This compound was prepared by the method of Example 22 from 4-carbamoyl-phenoxyacetone and DL-1-amino-3-(1-naphthoxy)propan-2-ol and isolated as the free base, m.p. 143—144°.

15 Analysis: Found — C, 69.8; H, 6.7; N, 6.8%
Calc'd for $C_{23}H_{26}N_2O_4$ — C, 70.0; H, 6.6; N, 7.1% 15

EXAMPLE 52

1-[2-(4-Carbamoylphenoxy)-1-methyl-ethylamino]-3-(2-phenylphenoxy)propan-2-ol.

This compound was prepared by the method of Example 22 from 4-carbamoylphenoxyacetone and DL-1-amino-3-(2-phenylphenoxy)propan-2-ol and isolated as the free base.

m.p. 158—160°

Analysis: Found — C, 70.9; H, 6.9; N, 6.2%
 calc'd for $C_{24}H_{28}N_2O_4$ — C, 71.4; H, 6.7; N, 6.7%

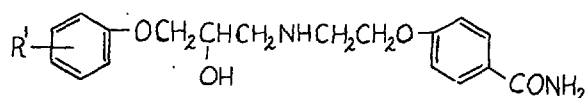
EXAMPLE 53

1-[2-(3-Carbamoyl-2-naphthoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol.

This compound was prepared by the method of Example 22 from 3-carbamoyl-2-naphthoxyacetone and DL-1-amino-3-(2-methylphenoxy)propan-2-ol and isolated as the free base, m.p. 106—108°.

Analysis: Found — C, 70.21; H, 7.0; N, 6.6%
 calc'd for $C_{24}H_{28}N_2O_4$ — C, 70.56; H, 6.9; N, 6.7%

The following compounds were prepared by the method of Example 4, from the appropriately substituted 1-phenoxy-2:3-epoxypropane and 2-(4-carbamoylphenoxy)-ethylamine, and isolated as the free base in each case.



Example	R ¹	m.p.	Analysis %		
			C	H	N
54	2-C ₆ H ₅ (2-phenyl)	124—125°	70.7 (70.9)	6.6 6.5	7.0 6.9
55	3-CH ₃	124—126°	66.1 (66.3)	7.2 7.0	8.4 8.1
56	2-OCH ₃	108—112°	63.2 (63.3)	6.9 6.7	7.9 7.8

EXAMPLE 57

1-[2-(4-Carbamoylphenoxy)ethylamino]-3-(1-naphthoxy)propan-2-ol.

This compound was prepared by the method of Example 4, from 1-(1-naphthoxy)-2:3-epoxypropane and 4-(2-aminooctoxy)benzamide, and isolated as the free base, m.p. 122—123°C.

Analysis: found — C, 69.2; H, 6.3; N, 7.4%
 calc'd for $C_{22}H_{24}N_2O_4$ — C, 69.5; H, 6.4; N, 7.4%

EXAMPLE 58

1-[N-Benzyl-2-(2-carbamoyl-4-methylphenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol.

1-(2-Methylphenoxy)-2,3-epoxypropane (13.8g), 1-(2-carbamoyl-4-methylphenoxy)-2-(benzylamino)-propane (25g), ethanol (250ml) and water (50ml) were heated together under reflux for six hours. The reaction mixture was evaporated and dried

in vacuo to give the free base of the desired product as a clear oil (39g.). This oil was then dissolved in the minimum quantity of chloroform and chromatographed on a column (80×3cm) packed with silicagel, using chloroform as the eluting solvent. The first 500ml of eluate was collected and the solvent removed *in vacuo* to give an oil which solidified after standing for two weeks. Repeated fractional recrystallisation of the solid from ethyl acetate, gave solid products A and B, m.p. 115 and 132°, respectively, which were the two racemic pairs of diastereoisomers of the product.

Analysis: Found for Product A: C, 72.29; H, 7.35; N, 6.20%
 for Product B: C, 72.31; H, 7.21; N, 6.06%
 Calc'd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06%

Hydrogenation of each of the products A and B of this Example, using a palladium-on-carbon catalyst, removes the N-benzyl group and yields one of the racemic pairs of diastereoisomers of the product of Example 22.

The activity of compounds of the invention as β -adrenergic blocking agents has been shown by their effectiveness in one or more of the following tests: (a) blocking the action of injected catecholamines on the isolated, perfused guinea-pig heart; (b) suppressing the tachycardia induced by isoprenaline in the anaesthetised rat or cat; (c) blocking the stimulating action of isoprenaline on the adenylyl cyclase enzyme present in rat heart muscle.

In test (a), force and rate of contraction, and flow rate through the coronary vessels, are measured. The responses to standard doses of one or more catecholamines are obtained, and the test compound is then administered. The catecholamines and test compounds are in all cases injected directly into the perfusing fluid immediately before entering the coronary vessels. The catecholamine doses are repeated and the extent of inhibition of the responses by the test compound is measured.

In test (b), groups of five urethane-anaesthetised rats are dosed with the test compound (2mg./kg.) subcutaneously. Heart rates are recorded before dosing and for thirty minutes after and the rats are then given a subcutaneous challenge of isoprenaline (0.1 mg./kg.). The degree of isoprenaline-induced tachycardia is recorded at fifteen minute intervals. Similarly, chloralosed cats are dosed with the test compound (0.1 to 1.0 mg./kg.) intravenously, and the effect of an isoprenaline challenge on heart rate is measured.

In test (c), homogenised rat heart in a standardised medium is incubated with adenosine-5'-triphosphoric acid (ATP) labelled with tritium, with and without isoprenaline, and the test compound is added at various concentrations to the homogenate with the isoprenaline. After incubation at 30°C, cyclic-3',5'-adenosine-monophosphoric acid (cyclic-AMP), containing a known proportion of carbon-14 labelled material, is added and synthesis of cyclic-AMP by the adenylyl cyclase enzyme is stopped by raising the temperature. Cyclic-AMP is separated and purified, and the amount synthesised in each case by the enzyme is measured as its tritium to carbon-14 ratio. The concentration of test compound which gives a 50% inhibition of the stimulating effect of isoprenaline on cyclic-AMP synthesis is taken as a measure of its activity.

By these criteria, the more active compounds have been found to be those in which R^3 is a carbamoyl (including N-substituted- and N-amino-carbamoyl, as hereinbefore described), carbamoyl-methyl, methoxycarbonyl or cyano group in the 2- or 4-position on a phenyl group, R^4 is hydrogen or a methyl group, R^5 and R^6 are each hydrogen, Y is oxygen and n is 1.

Further evaluation of these more active compounds has been carried out by assessing their activity in suppressing isoprenaline-induced tachycardia in dogs, the compound being administered intravenously and orally to conscious dogs at dose levels of 0.125 and 0.25 mg/Kg (intravenous) and 0.5 to 4mg/Kg (orally). These tests have shown that, of these compounds, the most active when administered orally are those in which R^1 is a methyl, methoxy or phenyl group in the 2-position on a phenyl group and R^3 is an unsubstituted carbamoyl group or a methoxycarbonyl group, provided that, when R^3 is in the 2-position on the phenyl group, then R^2 is a methyl or methoxy group in the 4,5- or 6- position.

The activity of compounds of the invention as anti-hypertensive agents has been shown by their effectiveness in lowering the blood pressure of conscious hypertensive rats or dogs, using a subcutaneous dose of 10mg./Kg. in the rat and an oral dose of 20mg./Kg. in the dog. Compounds having most activity in these tests are those in which R^3 is a carbamoyl or nitro group, R^4 is hydrogen or a methyl group, R^5 and R^6 are each hydrogen, Y is oxygen and n is 1 or 2.

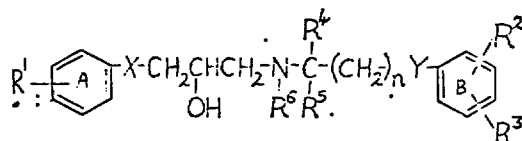
For administration to man, the dosage will depend on the purpose for which the compounds are administered, i.e. for the treatment of cardiac conditions such as angina pectoris, or for the treatment of hypertension, and also on the route of administration, i.e. oral or parenteral. It is expected, however, that oral dosages will be in the range from 0.5 to 4 mg/Kg/day for the treatment of cardiac conditions and from 2 to 10mg/Kg/day for the treatment of hypertension, such dosage being given in 3 or 4 divided doses per day. Dosages for intravenous administration would be expected to be about one-tenth of these in a single dose per day. Thus, for a typical adult patient (70 Kg), individual tablets or capsules might contain from 10 to 50 mg of active compound, and intravenous doses from 1 to 20 mg, in a suitable vehicle or carrier.

The compounds of the invention exist in D- and L- optically-active isomeric forms and the invention includes these forms as well as the racemic mixtures. Methods (1), (2) and (4) described above may be used to prepare optically-active isomers by using the appropriate substituted 2-propanol enantiomer as starting material, whereas method (3) will result in the production of racemic mixtures. Alternatively, the racemic product of any of the above methods may be resolved by well-known techniques, e.g. by fractional crystallisation of an addition salt formed with an optically-active acid.

Compounds of the invention in which R⁴ is not the same as R⁵ have two asymmetric centres and exist as two racemic pairs of diastereoisomers. In general, the products of each of the methods (1) to (4) described above, when R⁴ is not the same as R⁵, will be a mixture of the two pairs of stereoisomers, and these pairs may usually be separated from each other by physical methods, e.g. by fractional crystallisation or chromatography of the free bases or suitable salts, as shown in Examples 23 and 58. The invention includes the separated pairs, as well as mixtures thereof, as racemic mixtures or as separated D- and L-forms.

WHAT WE CLAIM IS:—

1. Compounds having the formula:



where: R¹ represents hydrogen, halogen, or a lower alkyl, phenyl, lower alkoxy or phenyl-substituted lower alkyl group;

R² represents hydrogen, or up to 2 halogen, lower alkyl or lower alkoxy substituents;

R³ represents an electron-withdrawing polar substituent as hereinbefore defined;

R⁴ and R⁵ each represent hydrogen or a lower alkyl group;

R⁶ represents hydrogen or a lower alkyl, lower alkanoyl or benzyl group;

either of the benzene rings A and B may be optionally substituted further by a —CH=CH—CH=CH— radical to form a naphthyl group;

X represents oxygen or sulphur;

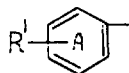
and either Y represents oxygen, sulphur, or a sulphinyl, sulphonyl or imino group as hereinbefore defined and n is 1, 2 or 3;

or Y represents a direct link and n is 0, 1, 2, 3 or 4;

the carboxylic acid esters and aldehyde condensation products as hereinbefore defined of such compounds, and their pharmaceutically acceptable acid addition salts.

2. Compounds as claimed in claim 1, in which X is oxygen.

3. Compounds as claimed in claim 1 or claim 2, in which



is a phenyl or substituted phenyl group.

4. Compounds as claimed in claim 3, in which R¹ is a methyl group in the 2-position.

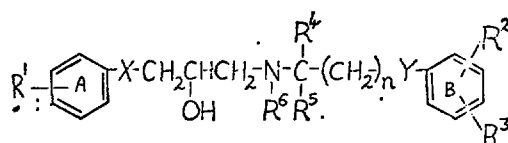
For administration to man, the dosage will depend on the purpose for which the compounds are administered, i.e. for the treatment of cardiac conditions such as angina pectoris, or for the treatment of hypertension, and also on the route of administration, i.e. oral or parenteral. It is expected, however, that oral dosages will be in the range from 0.5 to 4 mg/Kg/day for the treatment of cardiac conditions and from 2 to 10mg/Kg/day for the treatment of hypertension, such dosage being given in 3 or 4 divided doses per day. Dosages for intravenous administration would be expected to be about one-tenth of these in a single dose per day. Thus, for a typical adult patient (70 Kg), individual tablets or capsules might contain from 10 to 50 mg of active compound, and intravenous doses from 1 to 20 mg, in a suitable vehicle or carrier.

The compounds of the invention exist in D- and L- optically-active isomeric forms and the invention includes these forms as well as the racemic mixtures. Methods (1), (2) and (4) described above may be used to prepare optically-active isomers by using the appropriate substituted 2-propanol enantiomer as starting material, whereas method (3) will result in the production of racemic mixtures. Alternatively, the racemic product of any of the above methods may be resolved by well-known techniques, e.g. by fractional crystallisation of an addition salt formed with an optically-active acid.

Compounds of the invention in which R⁴ is not the same as R⁵ have two asymmetric centres and exist as two racemic pairs of diastereoisomers. In general, the products of each of the methods (1) to (4) described above, when R⁴ is not the same as R⁵, will be a mixture of the two pairs of stereoisomers, and these pairs may usually be separated from each other by physical methods, e.g. by fractional crystallisation or chromatography of the free bases or suitable salts, as shown in Examples 23 and 58. The invention includes the separated pairs, as well as mixtures thereof, as racemic mixtures or as separated D- and L-forms.

WHAT WE CLAIM IS:—

1. Compounds having the formula:



where: R¹ represents hydrogen, halogen, or a lower alkyl, phenyl, lower alkoxy or phenyl-substituted lower alkyl group;

R² represents hydrogen, or up to 2 halogen, lower alkyl or lower alkoxy substituents;

R³ represents an electron-withdrawing polar substituent as hereinbefore defined;

R⁴ and R⁵ each represent hydrogen or a lower alkyl group;

R⁶ represents hydrogen or a lower alkyl, lower alkanoyl or benzyl group;

either of the benzene rings A and B may be optionally substituted further by a —CH=CH—CH=CH— radical to form a naphthyl group;

X represents oxygen or sulphur;

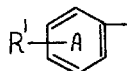
and either Y represents oxygen, sulphur, or a sulphinyl, sulphonyl or imino group as hereinbefore defined and n is 1, 2 or 3;

or Y represents a direct link and n is 0, 1, 2, 3 or 4;

the carboxylic acid esters and aldehyde condensation products as hereinbefore defined of such compounds, and their pharmaceutically acceptable acid addition salts.

2. Compounds as claimed in claim 1, in which X is oxygen.

3. Compounds as claimed in claim 1 or claim 2, in which

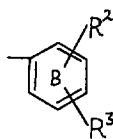


is a phenyl or substituted phenyl group.

4. Compounds as claimed in claim 3, in which R¹ is a methyl group in the 2-position.

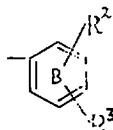


5. Compounds as claimed in any preceding claim in which



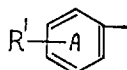
is a substituted phenyl group.

6. Compounds as claimed in any of claims 1 to 4, in which



is a substituted naphthyl group.

7. Compounds as claimed in any of claims 1, 2 or 5, in which



is a naphthyl group or a naphthyl group substituted on the A-ring.

8. Compounds as claimed in any preceding claim, in which R^4 is hydrogen or a methyl group, R^5 is hydrogen, Y is oxygen and n is 1.

9. Compounds as claimed in any preceding claim, in which R^2 is hydrogen, chlorine, a methyl or methoxy group or two methoxy groups and R^3 is a carbamoyl group.

10. Compounds as claimed in claim 8, in which R^3 is a carbamoyl, carbamoyl-methyl, methoxy-carbonyl or cyano group in the 2- or 4-position on a phenyl group.

11. Compounds as claimed in claim 10, in which R^1 is a methyl, methoxy or phenyl group in the 2-position on a phenyl group and R^3 is an unsubstituted carbamoyl group in the 2- position or 4-position on a phenyl group, provided that when R^3 is in the 2-position then R^2 is a methyl or methoxy group in the 4-, 5- or 6-position on the phenyl group.

12. Compounds as claimed in claim 1, in which R^3 is a carbamoyl or nitro group, R^4 is hydrogen or a methyl group, R^5 and R^6 are each hydrogen, Y is oxygen and n is 1 or 2.

13. 1-[2-(4-carbamoylphenoxy)ethylamino]-3-(2-methylphenoxy)propan-2-ol.

14. 1-[2-(4-carbamoylphenoxy)ethylamino]-3-(2-methoxyphenoxy)propan-2-ol.

15. 1-[2-(2-carbamoyl-4-methylphenoxy)ethylamino]-3-(2-methylphenoxy)propan-2-ol.

16. 1-[2-(2-carbamoyl-4-methylphenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol.

17. 1-[2-(2-carbamoyl-4-methoxyphenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol.

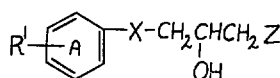
18. 1-[2-(2-carbamoyl-6-methylphenoxy)-1-methyl-ethylamino]-3-(2-methylphenoxy)propan-2-ol.

19. 1-[2-(4-carbamoylphenoxy)-1-methyl-ethylamino]-3-(2-phenylphenoxy)propan-2-ol.

20. 1-[2-(4-methoxycarbonyl-2,6-dimethylphenoxy)-1-methylethylamino]-3-(2-methylphenoxy)propan-2-ol.

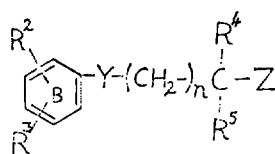
21. A compound as claimed in claim 1, substantially as described in any one of the Examples.

22. A method of preparing a compound as claimed in claim 1, which comprises reacting a compound of the formula:

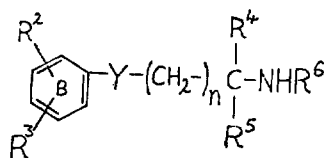


or



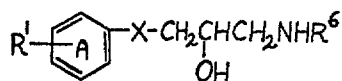


with an amine of the formula:



or

5

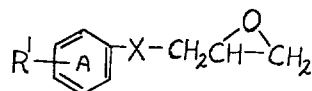


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respectively, where R^1 to R^6 , X , Y , n and rings A and B are as defined in claim 1 except that R^6 is not lower alkanoyl, and Z is halogen or a sulphonyloxy group.

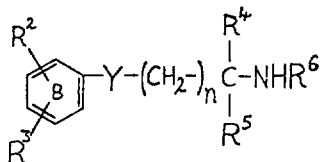
23. A method of preparing a compound as claimed in claim 1, which comprises reacting an epoxy compound of the formula:

10



10

with an amine of the formula:

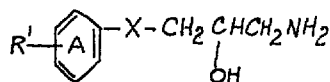


where R^1 to R^6 , X , Y , n and rings A and B are as defined in claim 1 except that R^6 is not lower alkanoyl.

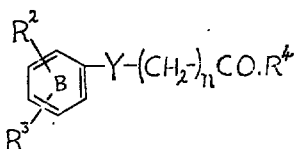
15

24. A method of preparing a compound as claimed in claim 1, in which R^3 and R^6 are each hydrogen, which comprises reacting an amine of the formula:

15



with an aldehyde or ketone of the formula:



20

where R^1 to R^4 , X , Y , n and rings A and B are as defined in Claim 1, to give the corresponding Schiff's base and reducing the latter with hydrogen in the presence of a hydrogenation catalyst, or with sodium borohydride.

20

25. A method according to claim 24, in which the amine is reacted with a ketone in which R^4 is a lower alkyl group.

25

26. A compound as defined in claim 1 when prepared by the method of any of claims 22 to 25.

25



27. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 21, or claim 26, and a pharmaceutical carrier or vehicle.

28. A tablet or capsule for oral administration comprising a composition as claimed in claim 27 including from 10 to 50 mg. of the compound.

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