

PATENT SPECIFICATION

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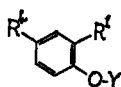


(54) PHENOXY-AMINES

(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 application relates to compounds having anti-histamine activity, and is particularly concerned with a novel class of ortho-substituted phenoxy-amines which have the property of blocking the actions of histamine at the so-called "H₂" receptor sites, e.g. those which influence gastric acid secretion, but have little or no ability to block the actions of histamine at the so-called "H₁" receptor sites, e.g. those which influence bronchial constriction.

The novel compounds of the invention have the general formula:



wherein R¹ represents an alkyl or cycloalkyl-alkyl group containing from 7 to 9 carbon atoms;

Y represents either (A) an aminoalkyl group of the formula —Alk—NR²R³, in which R² and R³ each represent a lower alkyl group or, together with the nitrogen atom to which they are attached, form a saturated heterocyclic group and 'Alk' represents a divalent saturated aliphatic hydrocarbon group containing from 2 to 4 carbon atoms, the free valences being located on different carbon atoms;

or (B) an amino-cyclic group of the formula —C_nH_{2n}—CH Z, in which n is 0 to 3 and

Z is a divalent group which completes a saturated heterocyclic ring containing at least one nitrogen atom and at least 4 carbon atoms, any such nitrogen atom being separated from the oxygen atom, to which the amino-cyclic group is attached, by a chain of from 2 to 4 carbon atoms; and R⁴ represents a hydrogen or halogen atom, or a lower alkyl, alkoxy or alkanoyl group, or an α-oximino-lower alkyl group; and the pharmaceutically acceptable acid addition salts of such compounds.

In this specification the term "lower", applied to a substituent group, means containing from 1 to 4 carbon atoms, and "halogen" means fluorine, chlorine, bromine or iodine.

In the general formula, R¹ may be a straight or branched chain alkyl group, or may be a cycloalkyl-alkyl group. For example, it may be a straight or branched chain heptyl, octyl or nonyl group, or a cyclohexyl-methyl, cyclohexyl-ethyl, cyclohexyl-propyl or cycloheptyl-ethyl group. Preferably, it is a primary hydrocarbyl radical, i.e. it is linked to the benzene ring by a methylene group. More preferably, it is a *n*-heptyl or 2-cyclohexyl-ethyl group.

When Y is a —Alk—NR²R³ group, R² and R³ may each be for example, a methyl, ethyl, propyl or butyl group, or together with the nitrogen atom may form, for example, a pyrrolidino, piperidino, morpholino, thiomorpholino piperazino, perhydroazepino or perhydrodiazepino group. When R² and R³ form with the nitrogen atom a saturated heterocyclic group which contains a further nitrogen atom, then such further nitrogen preferably carries a lower alkyl or benzyl group as substituent.

When Y is a —Alk—NR²R³ group, —Alk— may be, for example, an ethylene, propylene, ethyl-substituted ethylene, di-

methyl-substituted ethylene, trimethylene or tetramethylene group.

- When Y is a $-\text{C}_n\text{H}_{2n}-\text{CH} \text{---} \text{Z}$ group, $-\text{C}_n\text{H}_{2n}-$ may be, for example, a methylene, ethylidene, ethylene, propylene or trimethylene group, and the heterocyclic ring completed by Z may be, for example, a pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, perhydroazepine or perhydrodiazepine ring, provided that any nitrogen atom in the ring is separated by at least 2 carbon atoms from the oxygen atom to which the group is attached.

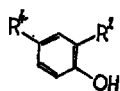
- Thus, $-\text{C}_n\text{H}_{2n}-\text{CH} \text{---} \text{Z}$ may be, for example, a 3-pyrrolidinyl or 3- or 4-piperidinyl group, a 2- or 3-pyrrolidinylmethyl or 2-, 3- or 4-piperidinylmethyl group, a 2-(2- or 3-pyrrolidinyl) ethyl or 2-(2- or 3-piperidinyl)-ethyl group, or a 3-(2-pyrrolidinyl)propyl or 3-(2-piperidinyl)propyl group. Any nitrogen atom in Z is preferably substituted with a lower alkyl or benzyl group while any carbon atom in $-\text{CH} \text{---} \text{Z}$ may be substituted with a lower alkyl group.

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

- Particularly preferred salts of compounds of this invention are the hydrochlorides and the addition salts formed with polycarboxylic acids, e.g. citric, tartaric, maleic, fumaric and oxalic acids.

PREPARATIVE METHODS

- (1) The compounds of the invention can be prepared from the appropriate ortho-substituted phenol, of the formula:

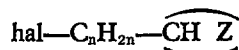


by

- (a) reaction with an alkali metal compound in an inert solvent to form the alkali metal phenate and then with the appropriate halide, of the formula:

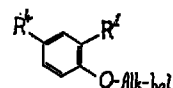


- or



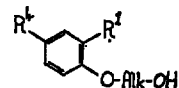
where 'hal' represents a halogen atom, to yield the required product direct;

- (b) reaction (under basic conditions) with a compound of the formula: $\text{hal}-\text{Alk}-\text{Q}$, where Q is halogen or other 'leaving' group, e.g. an aryl sulphonyloxy group, such as benzene sulphonyloxy or p-toluene sulphonyloxy, to form a compound of the formula:



which is then reacted with the appropriate secondary amine HNR^2R^3 ;

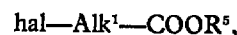
- (c) reaction with a halo-alkanol of the formula: $\text{hal}-\text{Alk}-\text{OH}$, under similar conditions to (b) to form a compound of the formula:



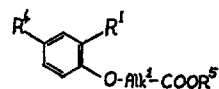
which is converted to the halide, e.g. by reaction with thionyl chloride, and then reacted with the appropriate secondary amine as in (b);

or

- (d) reaction with an alkali metal compound to form the phenate as in (a) and then with a lower alkyl ester of a halogeno-acid of the formula:



where R^5 is a lower alkyl group and 'Alk¹' is a saturated aliphatic hydrocarbon group containing up to 3 carbon atoms, to yield a compound of the formula:



which is then converted to the appropriate amide (optionally *via* the free acid and acid chloride) by reaction with the amine HNR^2R^3 , and finally reduced with lithium aluminium hydride to yield the required product.

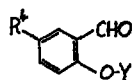
In the methods 1(a) and (d), the inert solvent may be, for example, toluene or dimethyl formamide. The formation of the phenate may be carried out by adding sodium hydride cautiously to the solution of the phenol and then heating. Reaction with the halide or halogeno-acid ester (e.g. the chloride or chloro-ester) may be carried out at reflux temperature.

In methods 1(b) and 1(c), the reaction of the phenol with the compound hal-Alk-Q or with the halo-alkanol (e.g. bromo-alkanol) may be carried out under reflux in methanolic potassium hydroxide, ethanolic sodium ethoxide or acetone/potassium carbonate solution.

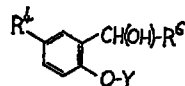
Subsequent reactions with the secondary amine may be carried out in any suitable inert solvent, e.g. ethanol, under reflux conditions. As a modification of these methods, a primary amine H_2NR^2 may be used instead of the secondary amine HNR^2R^3 , and the product alkylated in conventional manner to yield a compound of the invention in which R^2 and R^3 are each a lower alkyl group.

(2) Compounds of the invention in which R^1 is a primary hydrocarbyl radical, may also be prepared

(a) when R^4 is hydrogen, or a lower alkyl or alkoxy group, from a salicylaldehyde derivative of the formula:



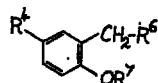
by the Grignard reaction with magnesium and a halide of the formula $hal-R^6$ where R^6-CH_2- is equivalent to R^1 , to yield a compound of the formula:



which is then reduced, e.g. with hydrogen in the presence of a suitable catalyst;

or

(b) when R^4 is hydrogen or a lower alkyl group, from a lower alkyl ether of salicylaldehyde itself, by similar reaction with the Grignard reagent and subsequent reduction, to yield a compound of the formula:

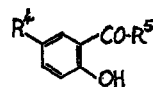


where R^7 is lower alkyl, the ether being converted to the free phenol by conventional methods and then reacted according to any of the preparations (1) (a), (b) or (c).

In the preparations (2) (a) and (b) the Grignard reagent is prepared in the usual way from magnesium and the appropriate halide in a suitable solvent, e.g. ether, and the appro-

priate aldehyde is then added slowly in the same solvent to the cooled solution of the Grignard reagent. The mixture is then heated to complete the reaction and the magnesium complex decomposed with acid at about 0° . The subsequent reduction may be carried out with hydrogen in the presence of a palladium-on-carbon catalyst in an acid medium, e.g. at 50° and 50 p.s.i. in ethanolic hydrochloric acid, or in the presence of Raney nickel as catalyst.

(3) Compounds in which R^1 is a primary hydrocarbyl radical and R^4 is hydrogen, halogen, or a lower alkyl or alkoxy group may also be prepared from ortho-acyl phenols of the formula:

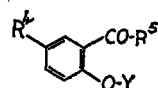


by

(a) reduction with zinc and hydrochloric acid, with hydrazine in a suitable solvent, or with hydrogen in the presence of a suitable catalyst, followed by reaction according to any of the preparations (1) (a), (b) or (c);

or

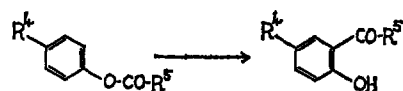
(b) reaction first according to any of the preparations (1) (a), (b) or (c) to yield a compound of the formula:



followed by reduction as in (a).

In each case, the reduction with hydrogen may be carried out as in preparation (2), and in the cases where R^4 is halogen R^4 may be simultaneously replaced by hydrogen.

The starting materials for preparation (3), i.e. acyl phenols of the afore-mentioned formula, can be readily prepared from the corresponding phenyl carboxylate by the Fries rearrangement reaction, with aluminium chloride or similar Lewis acid catalysts:



When R^4 is hydrogen, however, the reaction gives a mixture of *ortho* and *para* isomers which have to be separated to give the required *ortho*-acyl phenol.

In each preparation, the final product may

be obtained as free base by precipitation or by removal of solvent under reduced pressure, and purified by addition of water, extraction into a suitable solvent, drying, filtration and evaporation under reduced pressure. Acid addition salts may be obtained in the usual manner by addition of the appropriate acid in a suitable solvent to the liquid base, or to a solution thereof, and collection of the precipitate. Purification is carried out in the usual manner by recrystallisation from a suitable solvent.

The compounds of the invention have been found to be potent H_2 -antagonists, i.e. blockers of the action of histamine at H_2 receptor sites. This has been shown in tests in which their inhibiting effect on histamine-induced gastric acid secretion has been measured in experimental animals. In one of such tests, anaesthetised rats are sensitised by intravenous injection of carbachol (carbamoyl choline chloride) and are then injected intravenously with a standard dose of histamine and the pH of the gastric contents is measured over a short period, until it stabilises. The test compound is then administered, also intravenously, and the pH of the gastric contents is measured over a further period, until the inhibiting effect of the compound is no longer apparent. A 50% inhibition of the effect of histamine on pH, at a dose of 10 mg/Kg has been found for many of the compounds of the invention, while the most potent have a 100% inhibiting effect at 5 mg/Kg or a 50% inhibiting effect at 2.5 mg/Kg or even less. The more potent compounds are also effective over a period of 3 to 4 hours after injection. In a similar test with anaesthetised cats, histamine is continuously infused before and during administration of the test compound.

By virtue of their H_2 -blocking activity, the compounds of invention are useful for reducing gastric hyper-acidity and therefore in the treatment of gastric ulcers and other conditions caused or exacerbated by gastric hyper-acidity. They are also useful for relieving other

conditions due to the actions of histamine at H_2 receptor sites.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier 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 invention is illustrated by the following Examples in which the temperatures are given in $^{\circ}C$.

EXAMPLE 1

N,N - Diethyl - 2 - [2 - (2 - cyclohexyl - ethyl)phenoxy]ethylamine.

A 50% dispersion of sodium hydride (1.2g.) was added in portions to a stirred solution of 2 - (2 - cyclohexylethyl) phenol (5.0g.) in dry dimethylformamide (75ml.) and the mixture then heated to 100° for $\frac{1}{2}$ hour. 2 - (Diethylamino)ethyl chloride (3.3g) in dimethylformamide (25ml.) was slowly added, the mixture was refluxed for a period of 3 hours, then cooled and water (10 mls.) added. After evaporation of most of the solvent under reduced pressure, water (100mls.) was added to the residue and the mixture extracted twice with ether. The organic extract was washed with water, dried over sodium sulphate and filtered. Evaporation of the solvent then afforded the product as a pale yellow oil. Addition of an ethereal solution of citric acid gave a white precipitate of 9.1g. of the citrate salt of the product, which was recrystallised from isopropyl alcohol and had m.p. $130-131^{\circ}$.

Analysis: Found —

Calc'd for — $C_{26}H_{33}NO \cdot C_6H_8O_7$: C, 62.7; H, 8.2; N, 2.95%

C, 63.0; H, 8.3; N, 2.8%

EXAMPLES 2 TO 39

The compounds in Table I were prepared as in Example 1, from the appropriate substituted phenol and chloride Cl-Y. The

analytical figures required by the empirical formula of each compound are given in brackets. Salt formation was carried out in the usual way, using the appropriate acid.

TABLE I

Example	R ¹	Y	R ⁴	salt produced & m.p. (empirical formula)	Elemental analyses (%)		
					C	H	N
2	2-cyclohexyl-ethyl	$\text{—CH}_2\text{CHCH}_2\text{—}$ CH_3	H	oxalate 164—5° (C ₂₀ H ₃₃ NO.C ₂ H ₂ O ₄)	66.8; (67.1;	8.7; 8.9;	4.0 3.6)
3	"	$\text{—CH}_2\text{CH}_2\text{CH—}$	"	citrate 127—8° (C ₁₉ H ₃₁ NO.C ₆ H ₈ O ₇)	61.8; (62.3;	8.2; 8.2;	3.1 2.9)
4	<i>n</i> -heptyl	$\text{—CH}_2\text{CH}_2\text{—}$	H	citrate 94—5° (C ₁₇ H ₂₉ NO.C ₆ H ₈ O ₇)	60.3; (60.6;	8.3; 8.2;	2.6 3.1)
5	"	" $\text{—N(C}_2\text{H}_5)_2$	H	citrate 128—9° (C ₁₉ H ₃₃ NO.C ₆ H ₈ O ₇)	62.1; (62.1;	8.2; 8.5;	2.7 2.5)
6	"	$\text{—CH}_2\text{CH}_2\text{CH}_2\text{—}$ $\text{N(CH}_3)_2$	H	citrate 97—8° (C ₁₈ H ₃₁ NO.C ₆ H ₈ O ₇)	61.5; (63.0;	8.3; 8.3;	3.1 2.8)
7	"	$\text{—CH}_2\text{CHCH}_2\text{—}$ CH_3	H	citrate 79—79.5° monohydrate (C ₁₉ H ₃₃ NO.C ₆ H ₈ O ₇ .H ₂ O)	60.0; (60.0;	7.6; 8.6;	2.85 2.8)
8	"	$\text{—CH}_2\text{CH}_2\text{CH—}$ CH_3	H	oxalate 102—3° (C ₁₉ H ₃₃ NO.C ₂ H ₂ O ₄)	66.1; (66.1;	9.0; 9.2;	3.4 3.7)

TABLE I continued

					C	H	N
9	<i>n</i> -octyl	—CH ₂ CH ₂ CH ₂ —	N(CH ₃) ₂	H oxalate 120—120.5 (C ₁₉ H ₃₃ NO.C ₂ H ₂ O ₄)	66.2; (66.1;	9.2; 9.2;	3.2; 3.7)
10	<i>n</i> -nonyl	"	"	H citrate 95—6° (C ₂₀ H ₃₅ NO.C ₆ H ₈ O ₇)	62.4; (62.75;	8.3; 8.7;	2.7 2.8)
11	1-ethyl-hexyl	"	"	H citrate 110—2° (C ₁₉ H ₃₃ NO.C ₆ H ₈ O ₇)	61.8; (62.1;	8.5; 8.5;	2.7 2.9)
12	cyclohexyl-methyl	"	"	H citrate 121—3° (C ₁₈ H ₂₉ NO.C ₆ H ₈ O ₇)	61.6; (61.65;	7.6; 8.0;	3.0 3.0)
13	4,4-dimethyl-pentyl	—CH ₂ CH ₂ —	N(C ₂ H ₅) ₂	H citrate 130—130.5° (C ₁₉ H ₃₃ NO.C ₆ H ₈ O ₇)	62.6; (62.1;	8.4; 8.5;	2.7 2.9)
14	<i>n</i> -heptyl	—CH ₂ CH ₂ CH ₂ —	N(CH ₃) ₂	Cl oxalate 109—110° (C ₁₈ H ₃₀ ClNO.C ₂ H ₂ O ₄)	59.7; (60.1;	8.0; 7.6;	3.3 3.5)
15	"	"	"	CH ₃ oxalate 114—5° (C ₁₉ H ₃₃ NO.C ₂ H ₂ O ₄)	66.6; (66.1;	9.2; 9.2;	3.5; 3.7)
16	2-cyclohexyl-ethyl	—CH ₂ CH ₂ —	N(CH ₃) ₂	H hydrochloride 164° (C ₁₈ H ₂₉ NO.HCl)	69.0; (69.3;	9.7; 9.7;	4.2 4.5)

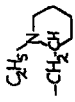
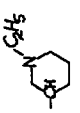
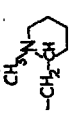
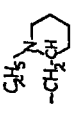
TABLE I Continued

				C	H	N
17	<i>n</i> -heptyl	$-\text{CH}_2\text{CH}_2-$	$-\text{N}(\text{C}_2\text{H}_5)_2$	citrate 145° $\text{C}_{19}\text{H}_{32}\text{ClNO} \cdot \text{C}_6\text{H}_8\text{O}_7$	58.3 (58.0)	7.7 7.7
18	2-propyl-pentyl	"	"	citrate 131—2° $(\text{C}_{20}\text{H}_{35}\text{NO} \cdot \text{C}_6\text{H}_8\text{O}_7)$	63.2 (62.75)	8.5 8.7
19	2-cyclohexyl-ethyl	"		oxalate 151—2° $(\text{C}_{21}\text{H}_{33}\text{NO} \cdot \text{C}_2\text{H}_2\text{O}_4)$	68.3 (68.1)	8.6 8.7
20	"	"	$-\text{N}(\text{C}_2\text{H}_5)_2$	citrate 145—6° $(\text{C}_{20}\text{H}_{32}\text{NOCl} \cdot \text{C}_6\text{H}_8\text{O}_7)$	59.0 (58.9)	7.5 7.6
21	"	"	$-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$	citrate 95—96° $(\text{C}_{22}\text{H}_{37}\text{NO} \cdot \text{C}_6\text{H}_8\text{O}_7)$	64.0 (64.2)	8.3 8.7
22	"	"	$-\text{N}(\text{C}_2\text{H}_5)_2$	citrate 118—118.5° $(\text{C}_{21}\text{H}_{35}\text{NO}_2 \cdot \text{C}_6\text{H}_8\text{O}_7)$	62.0 (61.7)	8.1 8.25
23	"		H	hydrochloride 162—162.5° $(\text{C}_{21}\text{H}_{33}\text{NO} \cdot \text{HCl})$	71.35 (71.65)	9.6 9.7
24	<i>n</i> -heptyl	$-\text{CH}_2\text{CH}_2-$	$-\text{N}(\text{C}_2\text{H}_5)_2$	citrate 135—136° $(\text{C}_{20}\text{H}_{35}\text{NO} \cdot \text{C}_6\text{H}_8\text{O}_7)$	63.0 (62.75)	8.3 8.7

TABLE I Continued

				C	H	N
25	2-cyclohexyl-ethyl	$\text{---CH}_2\text{CH}_2\text{---N}(\text{CH}_2\text{CH}_2)_2$	H	free base 202°/1mm (b.pt.) (C ₂₂ H ₃₇ NO)	79.4 (79.7)	11.3 11.25 3.9 4.2
26	"	$\text{---N}(\text{CH}_2\text{CH}_2)_2\text{---}$	H	citrate (hemi-hydrate) 106—107 (C ₂₀ H ₃₁ NO ₃ · $\frac{1}{2}$ H ₂ O·C ₆ H ₈ O ₇)	60.1 (60.2)	7.7 7.8 2.6 2.7
27	"	$\text{---N}(\text{CH}_2\text{CH}_2)_2\text{---}$	H	citrate 97—98° (C ₂₀ H ₃₁ NO·C ₆ H ₈ O ₇)	62.6 (63.3)	7.9 8.0 2.8 2.8
28	"	$\text{---N}(\text{CH}_2\text{CH}_2)_2\text{---}$	H	free base 199—201°/0.5mm (b.pt.) (C ₂₃ H ₃₇ NO)	81.1 (80.4)	11.2 10.9 3.8 4.1
29	"	$\text{---N}(\text{CH}_2\text{CH}_2)_2\text{---}$	H	citrate 159° (C ₂₁ H ₃₁ N ₂ O·C ₆ H ₈ O ₇)	62.2 (62.05)	7.7 8.1 5.6 5.4
30	"	$\text{---CH}_2\text{CH}_2\text{---N}(\text{CH}_2\text{CH}_2)_2$	H	citrate 112—113° (C ₂₁ H ₃₁ NO·C ₆ H ₈ O ₇)	63.5 (63.6)	8.4 8.5 2.8 2.75
31	"	$\text{---CHCH}_2\text{---N}(\text{CH}_2\text{CH}_2)_2$	H	citrate 139—40° (C ₂₁ H ₃₁ NO·C ₆ H ₈ O ₇)	63.6 (63.6)	8.4 8.5 2.75 2.75

TABLE I Continued

			C	H	N
32	2-cyclohexyl-ethyl		hydrochloride 187—188° H (C ₂₂ H ₃₅ NO.HCl.)	71.9 (72.2)	9.8 9.9 3.4 3.8)
33	<i>n</i> -nonyl	—CH ₂ CH ₂ —N(C ₂ H ₅) ₂	oxalate 121—122 H (C ₁₉ H ₃₃ NO.C ₈ H ₈ O ₄)	65.6 (66.1)	9.0 9.25 3.6 3.7)
34	2-cyclohexyl-ethyl	"	citrate 118—119° CH ₃ CO— (C ₂₂ H ₃₅ NO.C ₆ H ₈ O ₇)	62.4 (62.55)	7.9 8.1 2.4 2.6)
35	"		hydrochloride 159—160 H (C ₂₁ H ₃₃ NO.HCl.)	72.0 (71.7)	9.5 9.7 3.8 4.0)
36	"	—CH ₂ CH ₂ —N(C ₂ H ₅) ₂	citrate 129—130 F (C ₂₀ H ₃₂ FNO.C ₆ H ₈ O ₇)	61.0 (60.8)	8.1 7.85 2.4 2.7)
37	"		hydrochloride 170° H (C ₂₁ H ₃₃ NO.HCl.)	71.3 (71.65)	9.7 9.7 3.9 3.9)
38	cycloheptyl-methyl	—CH ₂ CH ₂ —N(C ₂ H ₅) ₂	citrate 149.5—150 H (C ₂₀ H ₃₃ NO.C ₆ H ₈ O ₇)	63.0 (63.0)	8.1 8.3 3.0 2.8)
39	cyclohexyl-methyl		citrate 137—138° H (C ₂₁ H ₃₃ NO.C ₆ H ₈ O ₇)	64.0 (63.9)	7.8 8.1 2.3 2.8)

EXAMPLE 40

(A) 1 - Bromo - 3 - (2 - *n* - heptylphenoxy)-
propane

- 5 2 - *n* - Heptylphenol (48 g.) was slowly
added to a stirred solution of potassium
hydroxide (14 g.) in methanol (100 ml.). 1,3-
Dibromopropane (202 g.) was then added
in one portion and the mixture refluxed on the
10 steam bath for 2 hours before cooling and
filtering the precipitated potassium bromide.
Evaporation of the solvent left a residual oil
which was distilled under reduced pressure,
the pure product being the fraction (36g.)
15 collected between 138° and 146° at 0.6 mm/
Hg pressure.

(B) 4 - [3 - (2 - *n* - heptylphenoxy)propyl] -
1 - methyl piperazine

The product of (A) (5.0g.) and N-methyl
piperazine (6.4g.) in ethanol (100 ml.) were
refluxed for 6 hours. After cooling and re-
20 moval of solvent under reduced pressure,
water (100 mls.) was added and the mixture
made just basic with 2N sodium hydroxide,
followed by extraction twice with ether. The
combined organic extracts were dried, filtered
25 and evaporated to give a residual oil that was
held for 1 hour at 60°C and 1 mm. pressure
in order to remove excess N-methyl piperazine.

The maleate salt was formed in the usual
manner and recrystallised from ethanol, to
30 yield 3.5g. of the di-maleate, m.p. 191—2°C.

Analysis: Found —

Calc'd for: $C_{21}H_{36}N_2O_2 \cdot 0.2C_4H_4O_4$ — C, 61.8; H, 7.7; N, 4.7%

C, 61.7; H, 7.85; N, 5.0%

EXAMPLES 41 TO 44

- 35 The compounds in Table II were prepared
as in Example 40 from the appropriate sub-
stituted phenol, 1,3-dibromopropane and the
appropriate amine, salt formation being carried

out in the usual way, using the appropriate
acid. In the case of Examples 41 and 44,
40 where the amine (diethylamine) is volatile,
reaction was carried out in a sealed bomb at
80°C instead of under reflux conditions.

TABLE II

Example	R ¹	Y	R ⁴	salt produced & m.p. (empirical formula)	Elemental Analysis (%)		
					C	H	N
41	n-heptyl	$\text{---CH}_2\text{CH}_2\text{CH}_2\text{---N}(\text{C}_2\text{H}_5)_2$	H	oxalate 91—2° ($\text{C}_{20}\text{H}_{35}\text{NO} \cdot \text{C}_2\text{H}_2\text{O}_4$)	66.8; (66.8)	9.1; 9.4	3.2 3.5
42	"	$\text{---N}(\text{CH}_2\text{C}_6\text{H}_5)_2$	H	di-hydrochloride 229—30° ($\text{C}_{27}\text{H}_{40}\text{N}_2\text{O} \cdot 2\text{HCl}$)	67.4; (67.3)	9.0; 8.8	5.3; 5.8
43	"	$\text{---N}(\text{C}_2\text{H}_5)_2$	H	oxalate 109—110° ($\text{C}_{20}\text{H}_{33}\text{NO} \cdot \text{C}_2\text{H}_2\text{O}_4$)	66.8; (67.1)	8.7; 9.0	3.3 3.6
44	2-cyclohexyl-ethyl	$\text{---N}(\text{C}_2\text{H}_5)_2$	H	citrate 135—6° ($\text{C}_{21}\text{H}_{35}\text{NO} \cdot \text{C}_6\text{H}_8\text{O}_7$)	63.8; (63.6)	8.1; 8.5	2.5; 2.75

EXAMPLE 45

The product of Example 34 was added to a solution of hydroxylamine hydrochloride (1.0g) and sodium acetate (2.0g.) in ethanol (50 ml). The mixture was stirred, warmed on the steam bath for 1½ hours and cooled. The ethanol was then evaporated off under reduced pressure and water (50 mls.) added to the residue, which was extracted twice with ether

(25 ml) evaporated and dried to give N,N-diethyl-2,2-(2-cyclohexylethyl)-4-(1-oximinioethyl)phenoxy]ethylamine, as a colourless oil.

Addition of ethereal citric acid gave the citrate salt, which was recrystallised from methanol/ethyl acetate as a white solid (1.8g), m.p. 111—113°.

20 Analysis: found —
calcd for $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2 \cdot \text{C}_6\text{H}_8\text{O}_7$ — C, 60.8; H, 7.8; N, 4.9%
C, 60.85; H, 8.0; N, 5.1%.

EXAMPLE 46

(1) Sodium hydride (50% dispersion, 4.8g) was added portionwise to a solution of 2 - (2 - cyclohexylethyl)phenol (20g) in dry dimethyl formamide (100ml) and the mixture heated to 80° for 1 hour. Ethyl chloroacetate (12.1g) was then added and the mixture refluxed for 4 hours, cooled, poured into water, extracted with ether, evaporated and dried in the usual manner. High vacuum distillation gave 14.1g of ethyl 2 - (2 - cyclohexyl - ethyl)phenoxyacetate as a clear liquid.

(2) This ester (25g) was added to ethanolic sodium hydroxide (150ml) and warmed overnight on the steam bath. It was then evaporated to 1/3 volume, added to water, extracted with ether, acidified with hydrochloric acid, extracted three times with chloroform (50 mls) and evaporated to give 18.5g. of crude 2 - (2 - cyclohexyl - ethyl)phenoxyacetic acid.

(3) The acid was treated with thionyl chloride, and the acid chloride so formed (4.0g) was slowly added in benzene (30mls) to a solution of *iso* butyl piperazine (2.0g.) in benzene (40ml.). A rapid reaction took place

and a gelatinous precipitate was formed. The mixture was refluxed on a steam bath for 1 hour, cooled and then evaporated to near dryness under reduced pressure. Water (100ml) was added to the residue, basified with NaOH and the mixture extracted with chloroform (50ml). Working up the chloroform extract in the usual manner afforded 4.6g of 1 - *iso*-butyl - 4 - [2 - (2 - cyclohexyl - ethyl)phenoxyacetyl]piperazine as a dark brown oil.

(4) This amide (4.6g) was slowly added to lithium aluminium hydride (1.1g) in dry ether (200ml.) and the mixture stirred and refluxed for 6½ hours. 5N aqueous sodium hydroxide solution (1.8ml.) was then added to decompose the excess LiAlH₄ and the mixture filtered. The filter cake was well washed with ether, the filtrates combined, dried and evaporated to give a mobile yellow oil. Addition of ethereal HCl gave 2.8g of 1 - *iso*butyl - 4 - [2 - (2 - {2 - cyclohexylethyl}phenoxy)ethyl]-piperazine di-hydrochloride, which was recrystallised from *isopropyl* alcohol, m.p. 255—6°.

Analysis: found:
calc'd for C₂₄H₄₀N₂O.2HCl:

C, 64.45; H, 9.3; N, 6.1%
C, 64.7; H, 9.5; N, 6.3%

EXAMPLE 47

(1) Cyclohexylmethylmagnesium bromide (35.4g, 0.2 moles) was prepared in ether (610 ml) in the usual manner from cyclohexylmethyl bromide and magnesium. 2-Diethylaminoethoxy benzaldehyde (44.2g; 0.2 moles) in ether (60 ml) was added slowly to the cooled Grignard reagent. At the completion of the addition the mixture was heated under reflux for 3 hours, and then decomposed with 5N hydrochloric acid in the presence of ice. The free base of the product was liberated by the addition of ammonium chloride (42.8g) and dilute ammonia and the separated ethereal layer removed. The aqueous phase was extracted twice further with ether (150ml total) and the ether extracts pooled and washed with dilute ammonia. Ether was removed by evaporation on a water bath and the residual oil distilled *in vacuo*. The fraction of b.p. 180—186/0.3mm (29.8g) was collected and shown to consist of 95% pure N,N - diethyl - 2 - [2 - (2 - cyclohexyl - 1 - hydroxyethyl)-phenoxy]ethylamine as free base.

(2) The product of (1) (20g) was dissolved in ethanol (100ml); 36%w/w hydrochloric acid (8ml) and 5% palladium on carbon catalyst (5g, i.e. 2.5g of catalyst wetted with an equal weight of water) were added. The suspension was hydrogenated at 50 p.s.i.g. and 50°C for 2½ hours, when hydrogen uptake ceased. Catalyst was filtered off and the filtrate was treated with an excess of 20% w/v sodium carbonate solution (50ml). Most of the remaining ethanol was removed by distillation *in vacuo* and the residue extracted with ether (3 × 50ml). Evaporation of the ether yielded 16.4g of N,N - diethyl - 2 - [2 - (2 - cyclohexylethyl)phenoxy]ethylamine as an oil. This was dissolved in ether (150ml) and a solution of citric acid monohydrate in ethyl methyl ketone (11.4g in 75ml) added slowly to the stirred solution. A colourless voluminous precipitate separated which was filtered, washed with ether and dried *in vacuo* at 40°C to yield 25.8g of the citrate, m.p. 128—130°, identical with the product of Example 1.

Analysis: Found:

calc'd for C₂₀H₃₃NO.C₆H₈O₇

C, 63.60; H, 8.50; N, 2.71%
C, 63.01; H, 8.34; N, 2.83%.

EXAMPLE 48

(1) 2 - Cyclohexylacetyl - 4 - chlorophenol (252.5g, 1.0 mole) in dimethylformamide (600 ml) was added over 1 hour to a suspension of sodium hydride oil dispersion (48g, 1.0 mole)

in dimethylformamide (400 ml) at 90° and the mixture obtained was stirred at 90—100° for a further 1½ hours. 2-Diethylaminoethylchloride (142g, 1.05 mole) in dimethylformamide (200 ml) was then added at 90° over 0.5 hours and

the reactants heated at 90—100° for 3 hours. After cooling the reaction to 25°, water (1 litre) was added cautiously, the solution obtained was extracted with chloroform (4 × 750 ml), the chloroform solution was backwashed with water (3 × 500 ml) and concentrated to an oil which was dissolved in dilute (5N) hydrochloric acid (750 ml) and backwashed with ether (3 × 250 ml). The aqueous solution was adjusted to pH 9.5 with sodium hydroxide solution and extracted with chloroform (3 × 250 ml). The chloroform solution on concentration gave 345g of *N,N* - diethyl - 2 - (2 - cyclohexylacetyl - 4 - chlorophenoxy)ethylamine as an oil. Purification of this product was achieved by formation of the citrate which was twice recrystallised

from isopropanol and had m.p. 123—125°.

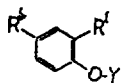
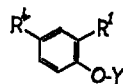
(2) The product of (1) as citrate (11.2g, 0.02 mole) dissolved in methylated spirit (100 mls) was hydrogenated over 10% palladium on carbon (6g) at 60 p.s.i.g. and 80° until hydrogen uptake was complete (2 hours). The catalyst was filtered off and the solution concentrated to an oil which was suspended in water, adjusted to pH 9.5 with sodium hydroxide solution and extracted with chloroform (3 × 50 mls). The chloroform solution was dried over magnesium sulphate and concentrated to an oil to yield 5g of *N,N* - diethyl - 2 - [2 - (2 - cyclohexylethyl) - phenoxy]ethylamine as free base, b.p. 183—9° at 3.5mm Hg. This was converted by conventional means to the hydrochloride, m.p. 161—2°.

Analysis: Found: C, 70.92; H, 10.12; N, 4.09; Cl, 10.75%
Calc'd for $C_{26}H_{33}NO \cdot HCl$: C, 70.78; H, 10.10; N, 4.13; Cl, 10.45%

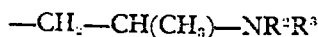
The products of all the Examples have been evaluated as H_2 -antagonists, in tests for effectiveness in inhibiting histamine-induced gastric acid secretion as described earlier in this specification. On the basis of the results obtained, the most effective compounds have been found to be those having the formula:

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which R^1 is a heptyl or 2-cyclohexyl-ethyl group, R^2 is a hydrogen or fluorine atom or a methyl or methoxy group, and Y is a group of the formula $-Alk-NR^2R^3$ or $-C_nH_{2n}-CH-Z$ (as hereinbefore defined) which contains (1) a single, tertiary nitrogen atom separated from the oxygen atom by a chain of two carbon atoms only, (2) a total of from 6 to 9 carbon atoms and (3) a methylene group attached to the oxygen atom. Thus Y is preferably, for example: a group of the formula $-CH_2-CH_2-NR^2R^3$ in which R^2 and R^3 together contain from 4 to 7 carbon atoms (e.g. the products of Examples 1, 5, 13, 19, 21, 22, 24, 25, 27, 28 and 36); a group of the formula



where R^2 and R^3 together contain from 3 to 6 carbon atoms (e.g. the product of Example 30); or a 1 - alkyl - 2 - piperidyl - methyl group in which the 1-alkyl substituent contains up to 3 carbon atoms (e.g. the products of Examples 32 and 37).

wherein R^1 represents an alkyl or cycloalkyl-alkyl group containing from 7 to 9 carbon atoms;

Y represents either (A) an aminoalkyl group of the formula $-Alk-NR^2R^3$, in which R^2 and R^3 each represent a lower alkyl group or, together with the nitrogen atom to which they are attached, form a saturated heterocyclic group and 'Alk' represents a divalent saturated aliphatic hydrocarbon group containing from 2 to 4 carbon atoms, the free valences being located on different carbon atoms;

or (B) an amino-cyclic group of the formula $-C_nH_{2n}-CH-Z$, in which n is 0 to 3 and

Z is a divalent group which completes a saturated heterocyclic ring containing at least one nitrogen atom and at least 4 carbon atoms, any such nitrogen atom being separated from the oxygen atom, to which the amino-cyclic group is attached, by a chain of from 2 to 4 carbon atoms;

and R^4 represents a hydrogen or halogen atom, or a lower alkyl, alkoxy or alkanoyl group, or an α -oximino-lower alkyl group; and the pharmaceutically acceptable acid addition salts of such a compound.

2. A compound as claimed in claim 1, in which R^1 is a primary hydrocarboyl radical.

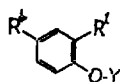
the reactants heated at 90—100° for 3 hours. After cooling the reaction to 25°, water (1 litre) was added cautiously, the solution obtained was extracted with chloroform (4 × 750 ml), the chloroform solution was backwashed with water (3 × 500 ml) and concentrated to an oil which was dissolved in dilute (5N) hydrochloric acid (750 ml) and backwashed with ether (3 × 250 ml). The aqueous solution was adjusted to pH 9.5 with sodium hydroxide solution and extracted with chloroform (3 × 250 ml). The chloroform solution on concentration gave 345g of *N,N* - diethyl - 2 - (2 - cyclohexylacetyl - 4 - chlorophenoxy)ethylamine as an oil. Purification of this product was achieved by formation of the citrate which was twice recrystallised

from isopropanol and had m.p. 123—125°.

(2) The product of (1) as citrate (11.2g, 0.02 mole) dissolved in methylated spirit (100 mls) was hydrogenated over 10% palladium on carbon (6g) at 60 p.s.i.g. and 80° until hydrogen uptake was complete (2 hours). The catalyst was filtered off and the solution concentrated to an oil which was suspended in water, adjusted to pH 9.5 with sodium hydroxide solution and extracted with chloroform (3 × 50 mls). The chloroform solution was dried over magnesium sulphate and concentrated to an oil to yield 5g of *N,N* - diethyl - 2 - [2 - (2 - cyclohexylethyl) - phenoxy]ethylamine as free base, b.p. 183—9° at 3.5mm Hg. This was converted by conventional means to the hydrochloride, m.p. 161—2°.

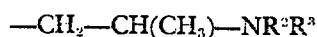
Analysis: Found: C, 70.92; H, 10.12; N, 4.09; Cl, 10.75%
Calc'd for $C_{20}H_{33}NO \cdot HCl$: C, 70.78; H, 10.10; N, 4.13; Cl, 10.45%

The products of all the Examples have been evaluated as H_2 -antagonists, in tests for effectiveness in inhibiting histamine-induced gastric acid secretion as described earlier in this specification. On the basis of the results obtained, the most effective compounds have been found to be those having the formula:



in which R^1 is a heptyl or 2-cyclohexyl-ethyl group, R^2 is a hydrogen or fluorine atom or a methyl or methoxy group, and Y is a group of the formula $-Alk-NR^2R^3$ or $-C_nH_{2n}-CH-Z$ (as hereinbefore defined) which contains (1) a single, tertiary nitrogen atom separated from the oxygen atom by a chain of two carbon atoms only, (2) a total of from 6 to 9 carbon atoms and (3) a methylene group attached to the oxygen atom.

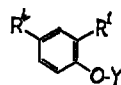
Thus Y is preferably, for example: a group of the formula $-CH_2-CH_2-NR^2R^3$ in which R^2 and R^3 together contain from 4 to 7 carbon atoms (e.g. the products of Examples 1, 5, 13, 19, 21, 22, 24, 25, 27, 28 and 36); a group of the formula



where R^2 and R^3 together contain from 3 to 6 carbon atoms (e.g. the product of Example 30); or a 1 - alkyl - 2 - piperidyl - methyl group in which the 1-alkyl substituent contains up to 3 carbon atoms (e.g. the products of Examples 32 and 37).

WHAT WE CLAIM IS:—

1. A compound of the formula:



wherein R^1 represents an alkyl or cycloalkyl-alkyl group containing from 7 to 9 carbon atoms;

Y represents either (A) an aminoalkyl group of the formula $-Alk-NR^2R^3$, in which R^2 and R^3 each represent a lower alkyl group or, together with the nitrogen atom to which they are attached, form a saturated heterocyclic group and 'Alk' represents a divalent saturated aliphatic hydrocarbon group containing from 2 to 4 carbon atoms, the free valences being located on different carbon atoms;

or (B) an amino-cyclic group of the formula $-C_nH_{2n}-CH-Z$, in which n is 0 to 3 and

Z is a divalent group which completes a saturated heterocyclic ring containing at least one nitrogen atom and at least 4 carbon atoms, any such nitrogen atom being separated from the oxygen atom, to which the amino-cyclic group is attached, by a chain of from 2 to 4 carbon atoms;

and R^2 represents a hydrogen or halogen atom, or a lower alkyl, alkoxy or alkanoyl group, or an α -oximino-lower alkyl group; and the pharmaceutically acceptable acid addition salts of such a compound.

2. A compound as claimed in claim 1, in which R^1 is a primary hydrocarboyl radical.



3. A compound as claimed in claim 2, in which R¹ is a *n*-heptyl or 2-cyclohexyl-ethyl group.
- 5 4. A compound as claimed in any preceding claim, in which R¹ is a hydrogen or fluorine atom or a methyl or methoxy group.
- 10 5. A compound as claimed in any preceding claim, in which Y contains (1) a single, tertiary nitrogen atom separated from the oxygen atom by a chain of two carbon atoms only, (2) a total of from 6 to 9 carbon atoms and (3) a methylene group attached to the oxygen atom.
- 15 6. A compound as claimed in claim 5, in which Y is a group of the formula —CH₂—CH₂—NR²R³ where R² and R³ are defined as in claim 1 and together contain from 4 to 7 carbon atoms.
- 20 7. A compound as claimed in claim 5, in which Y is a group of the formula —CH₂—CH(CH₃)—NR²R³ where R² and R³ are defined as in claim 1 and together contain from 3 to 6 carbon atoms.
- 25 8. A compound as claimed in claim 5, in which Y is a 1 - alkyl - 2 - piperidyl - methyl group in which the 1-alkyl substituted contains up to 3 carbon atoms.
- 30 9. N,N - diethyl - 2 - [2 - (2 - cyclohexyl - ethyl)phenoxy]ethylamine.
10. N,N - di - *n* - propyl 2 - [2 - (2 - cyclohexyl - ethyl)phenoxy]ethylamine.
11. N,N - diethyl - 2 - (2 - *n* - heptyl - phenoxy)ethylamine.
- 35 12. N,N - diethyl 2 - (2 - *n* - heptyl - 4 - methyl - phenoxy)ethylamine.
13. N,N - diethyl 2 - [2 - (4,4 - dimethyl-pentyl)phenoxy]ethylamine.
14. 1 - {2 - [2 - (2 - cyclohexyl - ethyl)-phenoxy]ethyl}piperidine.
15. 1 - {2 - [2 - (2 - cyclohexyl - ethyl)-phenoxy]ethyl}pyrrolidine.
16. 1 - {2 - [2 - (2 - cyclohexyl - ethyl)-phenoxy]ethyl} - 2,6 - dimethyl - piperidine.
17. N,N - di - ethyl - 2 - [2 - (2 - cyclohexyl - ethyl) - 4 - methoxy - phenoxy]ethyl-amine.
18. N,N - di - ethyl - 2 - [2 - (2 - cyclohexyl - ethyl) - 4 - fluoro - phenoxy]ethyl-amine.
19. N,N - diethyl - 2 - [2 - (2 - cyclohexyl - ethyl)phenoxy] - 1 - methyl - ethyl-amine.
20. 2 - [2 - (2 - cyclohexyl - ethyl)phenoxy-methyl] - 1 - ethyl - piperidine.
21. 2 - [2 - (2 - cyclohexyl - ethyl)phenoxy-methyl] - 1 - methyl - piperidine.
22. A pharmaceutically-acceptable acid-addition salt of a compound as claimed in any of claims 9 to 21.
23. A salt as claimed in claim 22, formed by the addition of hydrochloric acid.
24. A salt as claimed in claim 22 formed by the addition of a polycarboxylic acid.
25. A salt as claimed in claim 24, in which the acid is citric, tartaric, maleic, fumaric or oxalic acid.
26. A composition comprising a compound as claimed in any preceding claim and a pharmaceutically-acceptable carrier or diluent.
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Chartered Patent Agent,
Agent for the Applicants.

