United States Patent [19]

Köppe et al.

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[54] **1-PHENOXY-2-HYDROXY-3-ALKYLAMINO-PROPANES**

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[22] Filed: **Dec. 2, 1971**

[21] Appl. No.: **204,316**

Related U.S. Application Data

[63] Continuation of Ser. No. 781,985, Dec. 6, 1968, abandoned.

[30] **Foreign Application Priority Data**

Dec. 13, 1967 Germany 1643625

[52] **U.S. Cl.** ..... **260/465 E,** 260/340.5, 260/465 D, 260/471 A, 260/479 S, 260/519, 260/559 A, 260/570.7, 260/562 A, 424/282, 424/304, 424/309, 424/319, 424/324, 424/330

[51] **Int. Cl.** **C07c 121/78**

[58] **Field of Search** ..... 260/465 E

[56] **References Cited**

UNITED STATES PATENTS

3,459,782 8/1969 Koppe et al. 260/465

Primary Examiner—Lewis Gotts
Assistant Examiner—Dolph H. Torrence
Attorney, Agent, or Firm—Hammond & Littell

[57] **ABSTRACT**

The compounds are 1-phenoxy-2-hydroxy-3-alkylamino-propanes and non-toxic acid addition salts thereof, useful as β-adrenolytics and hypotensives in warm-blooded animals.

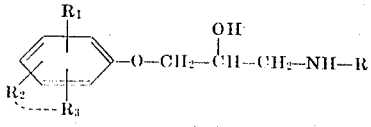
3 Claims, No Drawings

1-PHENOXY-2-HYDROXY-3-ALKYLAMINO-PROPANES

This is a continuation of Ser. No. 181,985, filed Dec. 6, 1968, now abandoned.

This invention relates to novel 1-phenoxy-2-hydroxy-3-alkylamino-propanes and their non-toxic acid addition salts, as well as to various methods of preparing these compounds.

More particularly, the present invention relates to a novel class of racemic or optically active compounds of the formula



(I)

wherein

R is alkyl of 5 to 8 carbon atoms comprising at least one quaternary carbon atom which is attached, directly or through an alkylene chain of 1 to 4 carbon atoms, to the amino nitrogen atom,

R_1 is cyano, carboxyl, hydroxyl, amino, nitro, trifluoromethyl, alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms, alkinyl of 2 to 5 carbon atoms, alkenyloxy of 2 to 5 carbon atoms, alkinyloxy of 2 to 5 carbon atoms, hydroxyalkyl of 1 to 5 carbon atoms, alkoxyalkyl of 2 to 5 carbon atoms, alkylaminoalkyl of 2 to 5 carbon atoms, dialkylaminoalkyl of 3 to 5 carbon atoms, alkylamino of 1 to 5 carbon atoms, cyanoalkyl of 2 to 5 carbon atoms, alkoxycarbonyl of 2 to 5 carbon atoms, alkylaminocarbonyl of 2 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, acyl, acyloxy, acylamino, (each of 1 to 5 carbon atoms) halogen or alkoxy of 1 to 5 carbon atoms in m- or p-position with respect to the propanolamino side chain,

R_2 is hydrogen, halogen, cyano, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or alkenyl of 2 to 4 carbon atoms,

R_3 is hydrogen, halogen, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms, and

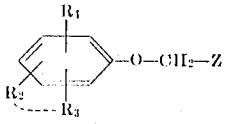
R_2 and R_3, together with each other, are 3,4-methylenedioxy,

with the proviso that R_1 is other than 2-bromo when R is 1,1-diethyl-butyl and R_2 and R_3 are hydrogen, and their non-toxic, pharmacologically acceptable acid addition salts.

The compounds of the formula I may be prepared by various methods involving well known chemical principles, among which the following have proved to be particularly efficient and convenient:

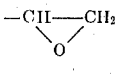
Method A

By reacting a compound of the formula



(II)

wherein R_1, R_2 and R_3 have the same meanings as in formula I and Z is



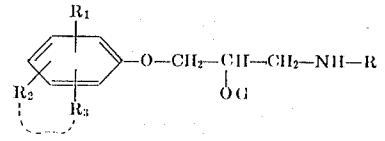
or —CH(OH)—CH_2—Hal, where Hal is halogen, with an alkylamine of the formula

$NH_2 - R$ III.

wherein R has the same meanings as in formula I, in a manner and under conditions which are customary for such reactions.

Method B

By splitting off an easily removable protective group from a compound of the formula

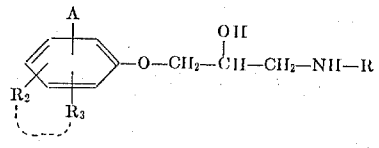


(IV)

wherein R, R_1, R_2 and R_3 have the same meanings as in formula I and G is a hydrolytically removable protective group, such as acyl or acetal.

Method C

By converting the substituent A in a compound of the formula



(V)

into a substituent R_1, as defined in formula I. R, R_2 and R_3 in formula V have the same meanings as in formula I, and A may have any one of the following meanings:

Aldehyde (—CHO), which is convertible into —CH_2OH or —CH_3 by reduction;

—$CONH_2$ or —CH=NOH, which are convertible into cyano by dehydration;

Haloalkyl, which is convertible into aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl or alkoxyalkyl by reaction with ammonia, an amine, water or aliphatic alcohols;

Hydroxyl, which is convertible into alkoxy by etherification;

Nitro, which is convertible into amino by reduction;

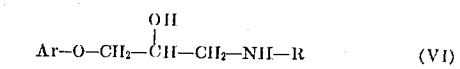
Alkoxycarbonyl, which is convertible into carboxyl by hydrolysis; or

Amino, which is convertible into cyano or halogen by diazotization and heating with copper(I)-cyanide or copper (I)-halide, respectively.

The conversion of a compound of the formula V into a compound of the formula I is effected by applying the required known reaction, i.e. dehydration exchange reaction, condensation, alkylation, reduction or diazotization and subsequent heating with a copper(I)-salt, etc., to the particular compound of the formula V.

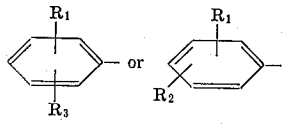
Method D

By introducing a halogen substituent into the phenyl ring of a compound of the formula



(VI)

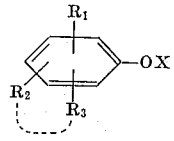
wherein R has the same meanings as in formula I, and Ar is



where R_1, R_2 and R_3 have the same meanings as in formula I. The introduction of the halogen substituent may be effected by reacting a compound of the formula VI with a mixture of concentrated hydrogen peroxide and the corresponding hydrohalic acid at elevated temperatures.

The starting compounds required for methods A through D are either known compounds or may be prepared according to known procedures.

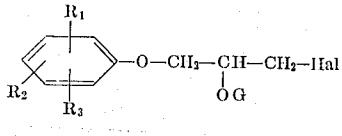
For instance, an epoxide of the formula II may be prepared by reacting epichlorohydrin with a corresponding phenol or phenolate of the formula



(VII)

wherein R_1, R_2 and R_3 have the same meanings as in formula I and X is hydrogen or a cation, especially an alkali metal cation. An epoxide of the formula II, in turn, may be used for the preparation of other starting compounds; for example, a halohydrin of the formula II may be prepared by reacting the corresponding epoxide with a hydrohalic acid.

A compound of the formula IV may be prepared by reacting a halohydrin of the formula II with a compound which forms a protective group G, such as vinyl ether or dihydropyran, and subsequently reacting the compound of the formula



(VIII)

formed thereby, wherein R_1, R_2 and R_3 and G have the same meanings as in formula IV and Hal is halogen, with an amine of the formula III.

Finally, compounds of the formulas V and VI may be prepared pursuant to method A described herein, i.e. starting from a corresponding phenol by way of the corresponding 1-phenoxy-2,3-epoxypropane and reaction of the latter with an alkylamine of the formula III.

The compounds according to the present invention comprise an asymmetric carbon atom and therefore occur as racemic mixtures as well as in the form of optically active antipodes. The latter may be obtained by separating the racemic mixture with the aid of customary auxiliary acids, such as dibenzoyl-D-tartaric acid or D-3-bromocamphor-8-sulfonic acid, or also by using the corresponding optically active starting compound.

The compounds of the formula I are organic bases and therefore form acid addition salts with inorganic or organic acids. Examples of non-toxic, pharmacologically acceptable acid addition salts are those formed with hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, maleic acid, acetic acid,

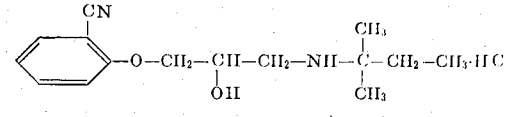
oxalic acid, lactic acid, tartaric acid, 8-chlorotheophylline and the like. Such acid addition salts may be obtained by conventional methods, for instance, by dissolving the free base in a suitable inert solvent and acidifying the solution with the desired inorganic or organic acid.

The following examples further illustrate the present invention and will enable others skilled in the art to understand it more completely. It should be understood, however, that the invention is not limited solely to the particular examples given below.

EXAMPLE 1

Preparation of 1-(o-cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane and its hydrochloride by Method A

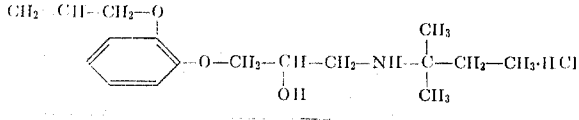
14 gm of 82% α,α-dimethyl-n-propyl-amine were added to a solution of 10.5 gm (0.06 mol) of 1-(o-cyano-phenoxy)-2,3-epoxy-propane in 80 cc of ethanol, the mixture was allowed to stand for 24 hours at 20°C., and thereafter it was refluxed on a boiling water bath for about 3 hours. Subsequently, the ethanol was distilled off in vacuo, the residue was digested with dilute hydrochloric acid, the insoluble matter was separated, and the acid solution was made alkaline with sodium hydroxide. The base precipitated thereby was taken up in ether, the organic phase was dried over magnesium sulfate, and the ether was distilled off. The residue, 1-(o-cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane, was dissolved in acetonitrile, the solution was acidified with ethereal hydrochloric acid, and the crystalline precipitate was recrystallized from ethanol/ether, yielding 7.6 gm of the colorless crystalline hydrochloride, m.p. 134°–136°C., of the formula



EXAMPLE 2

Preparation of 1-(o-allyloxy-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane and its hydrochloride by Method A

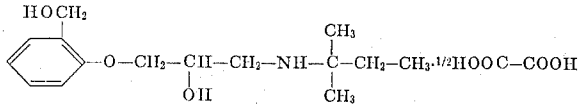
12.3 gm (0.06 mol) of 1-(o-allyloxy-phenoxy)-2,3-epoxy-propane were dissolved in 80 cc of ethanol, and 14 gm of 82% α,α-dimethyl-n-propyl-amine were added to the solution. The mixture was refluxed on a water bath for about three hours, and thereafter the reaction solution was evaporated to dryness in vacuo. The residue was dissolved in dilute hydrochloric acid, the solution was extracted with ether, the aqueous phase was made alkaline with sodium hydroxide, and the precipitated base was taken up in ether. The ethereal solution was dried, the ether was distilled off, and the residue, 14.8 gm of 1-(o-allyloxy-phenoxy)-2-hydroxy-3-[α,α-dimethyl-n-propyl)-amino]-propane, was dissolved in acetonitrile. The resulting solution was acidified with ethereal hydrochloric acid, ether was added to the acid solution, and the precipitate formed thereby was recrystallized from acetone/ether, yielding 11.5 gm of the hydrochloride, m.p. 65°–70°C., of the formula



EXAMPLE 3

Preparation of 1-(o-hydroxymethyl-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane and its oxalate by Method A

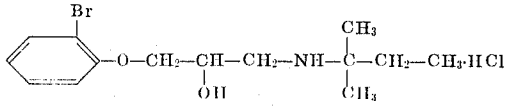
6.2 gm (0.036 mol) of 1-(o-hydroxymethyl-phenoxy)-2,3-epoxy-propane were dissolved in 60 cc of ethanol, 4.5 gm (0.052 mol) of 82% α,α-dimethyl-n-propyl-amine were added to the solution, and the mixture was refluxed for 3 hours. Thereafter, the ethanol was distilled off, the residue was dissolved in dilute hydrochloric acid, the aqueous solution was extracted with ether, the acid aqueous phase was made alkaline with sodium hydroxide, and the precipitated base was taken up in ether. The ethereal phase was dried, the ether was distilled off, and the residue, 9.3 gm of 1-(o-hydroxymethyl-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane, was dissolved in acetone. The resulting solution was acidified with a solution of 3.8 gm of oxalic acid in acetone, ether was added thereto, and the crystalline precipitate formed thereby was recrystallized from acetone, yielding 4.9 gm of the oxalate, m.p. 146°–149°C., of the formula



EXAMPLE 4

Preparation of 1-(o-bromo-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane and its hydrochloride by Method A

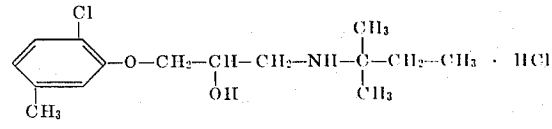
A solution of 8.7 gm (0.1 mol) of α,α-dimethyl-n-propyl-amine in 25 cc of ethanol was added to a solution of 11.45 gm (0.05 mol) of 1-(o-bromo-phenoxy)-2,3-epoxypropane in 75 cc of ethanol. The mixed solution was refluxed for 2 hours and was then worked up as described in Example 3. The precipitated base was dissolved in ethanol, the solution was acidified with ethereal hydrochloric acid, and the precipitate formed thereby was recrystallized from ethanol/ether, yielding 8.0 gm of the hydrochloride, m.p. 119°–122°C., of the formula



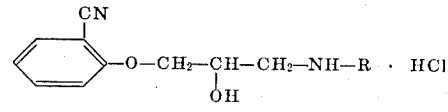
EXAMPLE 5

Preparation of 1-(2'-chloro-5'-methyl-phenoxy)-2-hydroxy-3-[(α, α-dimethyl-n-propyl)-amino]-propane and its hydrochloride by Method A

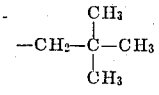
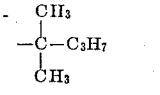
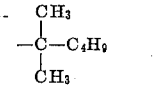
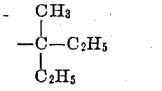
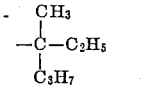
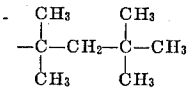
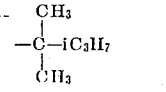
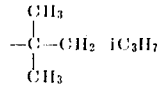
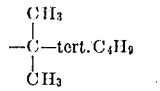
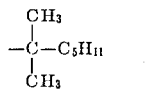
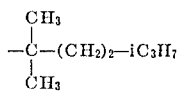
7.8 gm (0.04 mol) of 1-(2'-chloro-5'-methyl-phenoxy)-2,3-epoxy-propane were dissolved in 80 cc of ethanol, 8.7 gm (0.1 mol) of α,α-dimethyl-n-propyl-amine were added to the solution, and the mixture was refluxed for 3 hours. Thereafter, the ethanol was distilled off, the residue, 1-(2'-chloro-5'-methyl-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane, was taken up in dilute hydrochloric acid, and the solution was extracted several times with ether. The aqueous phase was evaporated to dryness in vacuo, and the residue was recrystallized twice from acetonitrile/ether, yielding 8.4 gm of the hydrochloride, m.p. 129°–131°C., of the formula



Using a procedure analogous to that described in Example 1, the following additional 1-(o-cyano-phenoxy)-2-hydroxy-3-alkylamino-propanes and their hydrochlorides of the formula

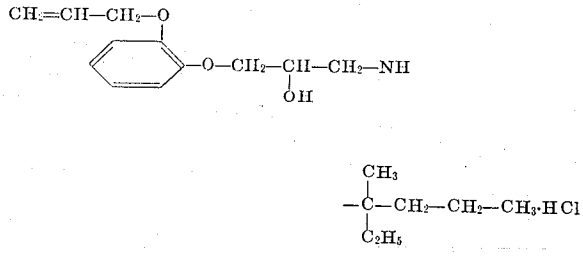


were prepared from 1-(o-cyano-phenoxy)-2,3-epoxy-propane and the corresponding primary amine of the formula III above:

Example No.	R	M.P. (hydrochloride), ° C.
6		163–165
7		131–132
8		148–150
9		144–147
10		154–157
11		145–148
12	$-C(C_2H_5)_3$	157–158
13		175–177
14		137–139
15		218–220
16		145–148
17		128–131

EXAMPLE 18

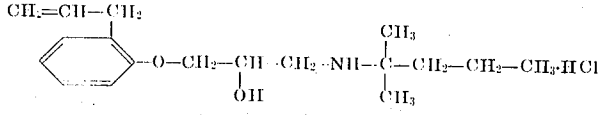
Using a procedure analogous to that described in Example 2, 1-(o-allyloxy-phenoxy)-2-hydroxy-3-[(α-methyl-α-ethyl-n-butyl)-amino]-propane hydrochloride, m.p. 89° – 92°C, of the formula



was prepared from 1-(o-allyloxy-phenoxy)-2,3-epoxy-propane and α-methyl-α-ethyl-n-butyl-amine.

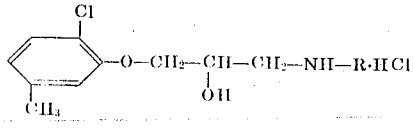
EXAMPLE 19

Using a procedure analogous to that described in Example 1, 1-(o-allyl-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane hydrochloride, m.p. 105° – 106°C, of the formula

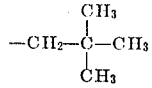
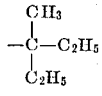
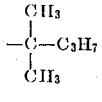
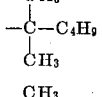
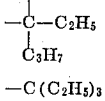


was prepared from 1-(o-allyl-phenoxy)-2,3-epoxy-propane and α,α-dimethyl-n-butyl-amine.

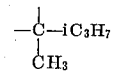
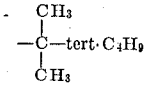
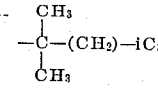
Using a procedure analogous to that described in Example 5, the following additional 1-(2'-chloro-5'-methyl-phenoxy)-2-hydroxy-3-alkylamino-propanes and their hydrochlorides of the formula



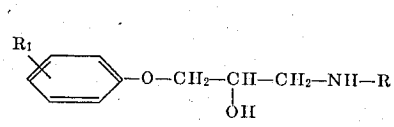
were synthesized from 1-(2'-chloro-5'-methyl-phenoxy)-2,3-propane and the corresponding primary amine of the formula III above:

Example No.	R	M.P. (hydrochloride), °C.
20		171–174
21		164–167
22		150–151
23		132–134
24		152–154
25	$-C(C_2H_5)_3$	201–203
26	CH_3	189–191

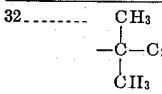
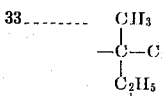
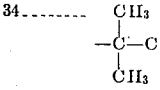
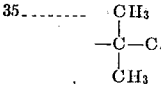
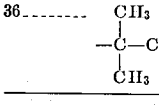
– Continued

Example No.	R	M.P. (hydrochloride), °C.
		
27		253–255
28		106–108
29	$-C(CH_3)_2-CH_2CH(CH_3)_2$	152–155
30	$-C(CH_3)_2-(CH_2)_4-CH_3$	102–104
31	$-C(CH_3)_2-CH_2-C(CH_3)_3$	174–176

Using a procedure analogous to that described in Example 1, the following additional 1-phenoxy-2-hydroxy-3-alkyl-amino-propanes and their hydrochlorides of the formula

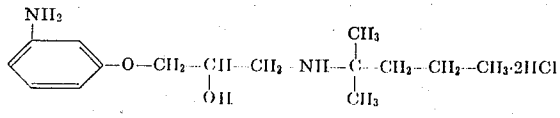


were prepared from the corresponding 1-phenoxy-2,3-propane and primary amine of the formula III:

Example No.	R	R_1	F.P. (hydrochloride), °C.
32		3-CN	139–141
33		4-CN	203–206
34		3-CH_3	124–126
35		4-C(=O)OCH_3	144–146
36		3-NO_2	140–142

EXAMPLE 37

By reduction of 1-(3'-nitro-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane (the free base product of Example 36) with catalytically activated hydrogen, 1-(3'-amino-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane was prepared, whose dihydrochloride of the formula

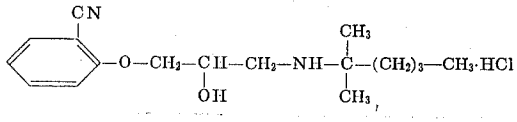


had a melting point of 173°- 174°C.

EXAMPLE 38

Preparation of 1-(o-cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-pentyl)-amino]-propane and its hydrochloride by method A

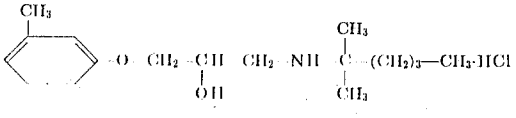
2.1 gm (0.087 mol) of 1-(o-cyano-phenoxy)-2-hydroxy-3-bromo-propane were dissolved in 50 cc of ethanol, 2 gm (0.0175 mol) of tert.heptylamine (α,α-dimethyl-n-pentylamine) were added to the solution, and the mixture was refluxed for two hours. Thereafter, the ethanol was distilled off, the residue was digested with dilute NaOH, the aqueous alkaline mixture was extracted with ether, the ethereal extract solution was washed with water and dried over magnesium sulfate, and the ether was distilled off. 3 gm of raw 1-(o-cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-pentyl)-amino]-propane remained behind, which were dissolved in a small amount of ethanol, the resulting solution was acidified with ethereal hydrochloric acid, and the precipitate formed thereby was recrystallized from ethanol/ether, yielding 2.8 gm of the hydrochloride, m.p. 144° - 145°C, of the formula



EXAMPLE 39

Preparation of 1-(m-tolyloxy)-2-hydroxy-3-[(α,α-dimethyl-n-pentyl)-amino]-propane and its hydrochloride by method B

500 mgm of 1-(m-tolyloxy)-2-hydroxy-3-[(α,α-dimethyl-n-penty)-amino]-propane tetrahydropyranyl ether were heated with 10 cc of concentrated hydrochloric acid for two hours on a boiling water bath. Thereafter, the reaction mixture was allowed to cool, was then made alkaline with sodium hydroxide, and the precipitated raw base, 1-(m-tolyloxy)-2-hydroxy-3-[(α,α-dimethyl-n-pentyl)-amino]-propane, was taken up in ether. The presence of the free aminoalcohol was confirmed by thin-layer chromatography of the ethereal solution. The solution was dried, evaporated, the residue was dissolved in a small amount of ethanol, and the solution was acidified with ethereal hydrochloric acid, whereby a small amount of the hydrochloride, m.p. 121° - 125°C, of the formula



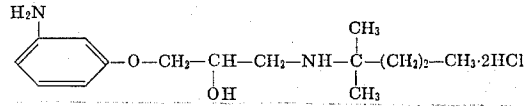
precipitated out.

The starting compound was prepared as follows: 4.6 gm (0.019 mol) of 1-(m-tolyloxy)-2-hydroxy-3-bromo-propane were slowly admixed with 1.6 gm of dihydropyran in the presence of a catalytic amount of p-toluene-sulfonic acid, whereby an exothermic reaction occurred. After about 15 minutes the reaction mixture was dissolved in 50 cc of ethanol, 2.2 gm (0.019 mol) of α,α-dimethyl-n-pentyl-amine were added to the solution, and the mixture was refluxed for 5 hours. Thereafter, the ethanol was distilled off, the residue was dissolved in ether, and the solution was acidified with an ethereal oxalic acid solution. After some time of standing the oxalate of 1-(m-tolyloxy)-2-hydroxy-3-[(α,α-dimethyl-n-pentyl)-amino]-propane tetrahydropyranyl ether, m.p. 118° - 122°C, began to crystalize out. 1.2 gm of the compound were isolated.

EXAMPLE 40

Preparation of 1-(m-amino-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane and its dihydrochloride by method C

7.1 gm (0.024 mol) of 1-(m-nitro-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane were hydrogenated at 20°C in 50 cc of methanol in the presence of Raney nickel. After absorption of the theoretical amount of hydrogen the catalyst was filtered off, the methanol was distilled out of the filtrate, and the residue, raw 1-(m-amino-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane, was dissolved in ethanol. The ethanolic solution was acidified with ethereal hydrochloric acid, and the crystalline precipitate formed thereby was recrystallized by dissolving it in ethanol and adding ether to the solution. 1.5 gm of the dihydrochloride, m.p. 173° - 174°C, of the formula

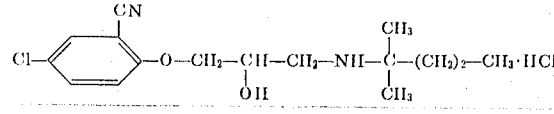


were obtained.

EXAMPLE 41

Preparation of 1-(o-cyano-p-chloro-phenoxy)-2-hydroxy-3-[(α-methyl-α-ethyl-n-butyl)-amino]-propane and its hydrochloride by method D

6.52 gm (0.02 mol) of 1-(o-cyano-phenoxy)-3-[(α-methyl-α-ethyl-n-butyl)-amino]-propane hydrochloride were dissolved in 55 cc of concentrated hydrochloric acid, and then 2.7 gm (0.024 mol) of 30% hydrogen peroxide were added dropwise to the solution at about 45°C, whereby the internal temperature rose to 65°C. The reaction mixture was thereafter stirred at 60°C for 30 minutes, then concentrated by evaporation in vacuo, made alkaline with dilute sodium hydroxide, and the oily product precipitated thereby was taken up in ether. The ethereal solution was washed with water, dried over magnesium sulfate, and evaporated to dryness in vacuo. The solid residue was dissolved in ethyl acetate and recrystallized therefrom by addition of petroleum ether. The pure crystalline base, 1-(o-cyano-p-chloro-phenoxy)-2-hydroxy-3-[(α-methyl-α-ethyl-n-butyl)-amino]-propane, was dissolved in ether, and the resulting solution was acidified with ethereal hydrochloric acid. The precipitate formed thereby was collected and recrystallized from acetonitrile/ether, yielding 2 gm of the hydrochloride, m.p. 143° - 145°C, of the formula

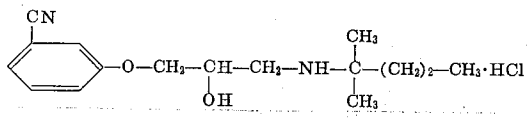


EXAMPLE 42

Preparation of 1-(m-cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane and its hydrochloride by method C

3.39 gm (0.01 mol) of 1-(m-amino-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane hydrochloride were dissolved in 3.5 of concentrated

hydrochloric acid, and the solution was diluted with 20 cc of water. The aqueous solution was cooled to 10°C, and then, while stirring, a solution of 1.4 gm (0.02 mol) of $NaNO_2$ in 10 cc of water was added dropwise over a period of 15 minutes. Thereafter, the mixture was stirred for 30 minutes more at 10°C, and then a solution of 5 gm of $CuSO_4 . 5H_2O$ and 5.6 gm of potassium cyanide in 30 cc of water, heated to 90°C, was added dropwise to the mixture at 80°–90°C over a period of 20 minutes, accompanied by stirring. Subsequently, the aqueous phase was decanted from resinous components which had formed and was then extracted with chloroform. The organic phase was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue, raw 1-(m-cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-butyl)-amino]-propane, was dissolved in a small amount of ethanol, the solution was acidified with ethereal hydrochloric acid, and the crystalline precipitate formed thereby was recrystallized from ethanol/ether, yielding 0.7 gm of the hydrochloride, m.p. 138° – 140° C of the formula



The compounds according to the present invention, that is, those embraced by formula I above and their nontoxic, pharmacologically acceptable acid addition salts, have useful pharmacodynamic properties. More particularly, they exhibit β-adrenolytic and hypotensive activities in warm-blooded animals, as confirmed by in vivo tests on guinea pigs. Thus, the compounds of the invention are useful for the treatment and prophylaxis of diseases of the coronary heart vessels and cardiac arrythmia, especially tachicardia, in warm-blooded animals.

For pharmaceutical purposes the compounds according to the present invention are administered to warm-blooded animals perorally or parenterally as sole active ingredients or in combination with other pharmacodynamically active ingredients, such as coronary dilators or sympathicomimetics, in customary dosage unit compositions, that is, compositions in dosage unit form consisting essentially of an inert pharmaceutical carrier and one effective dosage unit of the active ingredient, such as tablets, coated pills, capsules, wafers, powders, solutions, suspensions, emulsions, syrups, suppositories and the like. One effective dosage unit of the compounds according to the present invention is from 0.0166 to 5.0 mgm/kg body weight, preferably 0.083 to 1.67 mgm/kg (peroral) or 0.0166 to 0.34 mgm/kg (parenteral).

The following examples illustrate a few dosage unit compositions comprising a compound of the instant invention as an active ingredient and represent the best mode contemplated of putting the invention to practical use. The parts are parts by weight unless otherwise specified.

EXAMPLE 43

Tablets

The tablet composition was compounded from the following ingredients:

	Parts
1-(o-Cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane hydrochloride	40.0
Corn starch	164.0
Secondary calcium phosphate	240.0
Magnesium stearate	1.0
Total	445.0

Compounding procedure:

The individual ingredients were intimately admixed with each other, the mixture was granulated in customary fashion, and the granulate was pressed into 445 mgm-tablets. Each tablet contained 40 mgm of the phenoxy-amino-propanol compound and, when administered perorally to a warm-blooded animal of about 60 kg body weight in need of such treatment, produced very good β-adrenolytic effects.

EXAMPLE 44

Gelatin capsules

The capsule filler composition was compounded from the following ingredients:

	parts
1-(o-Cyano-phenoxy)-2-hydroxy-3-[(α, α-dimethyl-n-butyl)-amino]-propane hydrochloride	25.0
Corn starch	175.0
Total	200.0

Compounding procedure:

The ingredients were intimately admixed with each other, and 200 mgm-portions of the mixture were filled into gelatin capsules of suitable size. Each capsule contained 25 mgm of the phenoxy-amino-propanol compound and, when administered perorally to a warm-blooded animal of about 60 kg body weight in need of such treatment, produced very good β-adrenolytic effects.

EXAMPLE 45

Hypodermic solution

The solution was compounded from the following ingredients:

1-(2'-Chloro-5'-methyl-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane hydrochloride	25	parts	
Sodium salt of EDTA	2	do.	
Distilled water q.s.ad	1000	do.	by vol.

Compounding procedure:

The propanol compound and the EDTA salt were dissolved in a sufficient amount of distilled water, and the solution was diluted to the indicated volume with additional distilled water, filtered until free from suspended particles, and filled into 1 cc-ampules under aseptic conditions, which were finally sterilized and sealed. Each ampule contained 25 mgm of the phenoxy-amino-propanol compound, and when the contents thereof were administered intravenously to a warmblooded animal of about 60 kg body weight in need of such treatment, very good β-adrenolytic effects were produced.

EXAMPLE 46

Sustained release pills

The pill core composition was compounded from the following ingredients:

	Parts
1-(o-Allyloxy-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane hydrochloride	25.0
Carboxymethyl cellulose (CMC)	295.0
Stearic acid	20.0
Cellulose acetate phthalate (CAP)	40.0
Total	380.0

Compounding procedure:

The propanol compound, the CMC and the stearic acid were intimately admixed with each other, the mixture was granulated in customary fashion with a solution of the CAP in 200 cc of a mixture of ethanol and ethyl acetate, and the granulate was pressed into 380 mgm-pill cores which were then coated with a sugar-containing 5% solution of polyvinylpyrrolidone in water. Each pill contained 25 mgm of the phenoxy-aminopropanol compound and, when administered perorally to a warm-blooded animal of about 60 kg body weight in need of such treatment, produced very good β-adrenolytic effects.

EXAMPLE 47

Tablets with combination of active ingredients

The tablet composition was compounded from the following ingredients:

	Parts
1-(o-Cyano-phenoxy)-2-hydroxy-3-[(α,α-dimethyl-n-propyl)-amino]-propane hydrochloride	35.0
2,6-Bis-(diethanolamino)-4,8-di-piperidino-pyrimido[5,4-d]-pyrimidine	75.0
Lactose	164.0
Corn Starch	194.0
Colloidal silicic acid	14.0
Polyvinylpyrrolidone	6.0
Magnesium stearate	2.0
Soluble starch	10.0
Total	500.0

Compounding procedure:

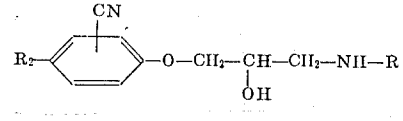
The propanol compound, the lactose, the corn starch, the colloidal silicic acid and the polyvinylpyrrolidone were intimately admixed with each other, the mixture was granulated in customary fashion with an aqueous solution of the soluble starch, the granulate was admixed with the magnesium stearate, and the composition was pressed into 500 mgm-tablets. Each tablet contained 35 mgm of the phenoxy-aminopropanol compound and 75 mgm of the pyrimidopyrimidine compound and, when administered perorally to a warm-blooded animal of about 60 kg body weight in need of such treatment, produced very good β-adrenolytic and coronary dilating effects.

Analogous results were obtained when an equal amount of any one of the other compounds embraced by formula I above was substituted for the particular phenoxy-aminp-propanol compounds in Examples 43 through 47. Likewise, the amount of active ingredient in these examples may be varied to achieve the dosage unit range set forth above, and the amounts and nature of the inert pharmaceutical carrier ingredients may be varied to meet particular requirements.

While the present invention has been illustrated with the aid of certain specific embodiments thereof, it will be readily apparent to others skilled in the art that the invention is not limited to these particular embodiments, and that various changes and modifications may be made without departing from the spirit of the invention or the scope of the appended claims.

It is claimed:

1. A compound of the formula



wherein

R is branched alkyl of 5 to 8 carbon atoms containing a quaternary carbon atom which is attached, directly or through an alkylene chain of 1 to 4 carbon atoms, to the amino nitrogen atom, and

R_2 is hydrogen or chlorine,

or a non-toxic, pharmacologically acceptable acid addition salt thereof.

2. A compound according to claim **1**, which is 1-(o-cyano-phenoxy)-2-hydroxy-3-[(αα-dimethyl-n-propyl)-amino]-propane or a non-toxic, pharmacologically acceptable acid addition salt thereof.

3. A compound according to claim **1**, which is 1-(o-cyano-phenoxy)-2-hydroxy-3-[(αα-dimethyl-n-butyl)-amino]-propane or a non-toxic, pharmacologically acceptable acid addition salt thereof.

* * * * *