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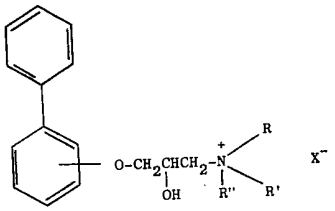
(19)

(54) NEW QUATERNARY AMMONIUM COMPOUNDS HAVING PHARMACOLOGICAL ACTIVITY

(71) THE REGENTS OF THE UNIVERSITY OF MICHIGAN, a constitutional corporation organized under the statutes of the State of Michigan, one of the United States of America, of Ann Arbor, Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel chemical compounds of the following formula:



(I)

wherein R, R′ and R″ are alkyl radicals containing from 1 to 4 carbon atoms and X^- is the anion of a pharmaceutically acceptable non-toxic acid.

Preferred among those compounds are those in which R and R′ are methyl and R″ is isopropyl. Especially preferred are those compounds in which R and R′ are methyl, R″ is isopropyl, X^- is halide, and the phenylphenoxy substituent is 2-phenylphenoxy.

Anions of suitable pharmaceutically acceptable non-toxic acids are typified by the halides, *e.g.* chloride, bromide, iodide, fluoride, the ortho, metal and pyrophosphates, the sulphate and the arylsulphate wherein the alkyl radical contains 1 to 4 carbon atoms which is typified by the methylsulphate and ethyl sulphate, benzenesulfonate, toluenesulfonate, acetate, lactate, succinate, maleate, tartrate, citrate, gluconate, ascorbate, benzoate and cinnamate. Other salts would preferably be prepared from these salts by ion exchange procedure.

Particularly preferred anions for the purpose of this invention are the iodide and the chloride.

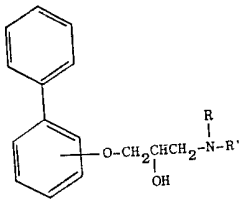
Insofar as quaternary ammonium salts of polybasic acids are contemplated as lying within the ambit of the invention, it should be understood that, in such a case, X^- represents a notional fraction of an anion of a polybasic acid, which anion partner may alternatively be designated

$$\frac{1}{n}(X^{-n})$$

wherein n denotes the toxicity.

The alkyl groups comprehended are the straight chain or branched groups having 1—4 carbon atoms inclusive as illustrated by methyl, ethyl, propyl, isopropyl, and the like.

The compounds of the present invention are conveniently prepared by reacting tertiary amines of the general formula



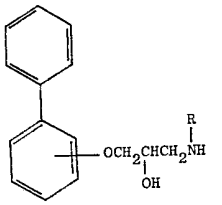
(II)

wherein R and R′ are alkyl radicals containing from 1 to 4 carbon atoms with a compound of the general formula

(alkyl)X

wherein the alkyl group contains 1 to 4 carbon atoms and X is a halide to give the quaternary compounds of formula I.

An alternate method for the preparation of the compounds of the present invention involves the reaction of a secondary amine of the general formula



(III)

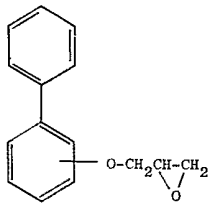
wherein R is defined as before with 2 molecular equivalents of a compound of the general formula

(alkyl)X

wherein alkyl and X are defined as before in connection with the reaction of a single molecular equivalent of (alkyl)X with a compound of general formula (II).

It should be apparent to those skilled in the art that when the first equivalent of the alkyl halide reacts with the secondary amine of formula (III), the tertiary amine of formula (II) is formed. Thus, this alternate method employs the compounds of formula (II). Whichever of these two methods is used, the compound (alkyl)X is preferably methyl chloride of methyl iodide.

The starting materials for the preparation of the instant compounds are prepared by reacting (2, 3 or 4)-phenylphenol with epichlorohydrin and aqueous alkali, e.g. sodium or potassium hydroxide, to produce intermediates of the formula



(IV)

These intermediates are allowed to react with a primary alkyl amine at reflux to afford the corresponding secondary amines of the formlu (III). These intermediates can also be reacted with an appropriate secondary amine to afford the corresponding tertiary amines of formula (II).

It is apparent that analogous methods of preparation, wherein for example, the methyl groups are added initially, followed by addition of the isopropyl moiety, are available by proper choice of the particular amine at each appropriate stage of the synthesis.

The compounds of the present invention are useful in consequence of their ability to reverse cardiac arrhythmias. They possess, moreover, the advantages of long-acting activity, and they are effective against cardiac rhythm disturbances associated with myocardial ischemia and infarction. These agents are, furthermore, advantageeously useful as compared to known anti-arrhythmic agents in that they unexpectedly lack the undesirable β-adrenergic receptor blocking activity of related prior art compounds. A further advantage of the compounds of this invention is their lack of local anesthetic activity and relative lack of persistent cardiovascular depressant effects. The above-described properties are demonstrated in the following assays:

LOCAL ANESTHETIC ACTIVITY: Female frogs (Rana pipiens) are decapitated and the sciatic-tibialperoneal nerves (sciatic trunk) are removed bilaterally and placed in frog Ringer's solution. The Ringer's solution is of the following composition, expressed as millimoles per liter: NaCl, 111; KCl, 2.7; $CaCl_2 . 2H_2O$, 1.4; and $NaHCO_3$, 2.4. The solution has a pH of 7.4 and is maintained at a temperature of 25°C. In one series of experiments the epineurium of the nerve is removed by the method of Feng and Liu, *J. Cell. Comp. Physiol.* 34, 1 (1949).

The experimental design has been described in greater detail previously by Lucchesi and Iwami, *J. Pharmacol. Exp. Therap., 162,* 49 (1968). Briefly, a sciatic trunk is passed through a plastic T-tube, and both are mounted on platinum electrodes in a nerve chamber with a humidified atmosphere. Ringer's solution can then be pumped at a constant rate into the vertical limb of the T-tube. The pump also serves to remove fluid from the chamber at this same rate.

Monophasic spikes are recorded by crushing that part of the nerve in contact with the distal recording electrode. The nerves are stimulated at their peripheral ends so as to produce a maximal spike potential for the A α group of fibers. Since the height of the spike is an index of the number of fibers conducting impulses, and since the response is maximal, any reduction in spike height can be attributed to a block of some fibers in the treated segment. The action potential is amplified through a preamplifier, displayed on an oscilloscope and photographed. Spike potentials are photographed every 15 min. for 1 hour, starting with the time drugs are applied to the nerve trunks. The percent change from control spike amplitude is calculated from the photographed tracings.

TESTS FOR BET-ADRENERGIC RECEPTOR BLOCKADE: Dogs, 9.2—12.8 kg, are anesthetized with intravenous pentobarbital sodium, 30 mg/kg. The right ventricle is exposed through the 5th right intercostal space; the pericardium is opened and a calibrated Walton-Brodie strain-gauge arch is sutured to the right ventricle. The muscle segment between the feet of the strain-gauge arch is stretched to a length which gives a contraction of maximal amplitude. The animals are respired with room air by means of a Harvard Respirator. Femoral arterial pressure is measured with a Statham P23dB pressure transducer. Heart

rate is recorded with a Grass tachometer which is triggered by the electrical signal from the strain-gauge arch. Recordings are made on a Grass model 7 polygraph. All drugs are administered *via* a cannulated jugular vein.

Changes in heart rate and right ventricular isometric force to geometrically increasing doses of isoproterenol administered intravenously are determined before and after administration of test compound. Each dog thus serves as its own control. Statistical analysis of the data is performed by the method of paired comparisons as described by Hill (1961).

STUDIES OF CARDIOVASCULAR EFFECTS OF TEST COMPOUND — HEMO DYNAMIC MEASUREMENTS: Dogs (13.6 to 17.0 kg), are anesthetized with intravenous pentobarbital sodium, 30 mg/kg. Positive pressure respiration is maintained with a Harvard respirator. The cervical vagi are severed and the jugular vein is cannulated for administration of drugs. The thorax is entered through the fourth right intercostal space; the pericardium is opened and sutured to the chest wall to form a cradle to support the heart. A calibrated Walton-Brodie strain gauge arch is sutured to the right ventricle. Heart rate is recorded by means of a cardiotachometer which is triggered by the electrical signal from the strain gauge arch. Blood pressure is measured from a cannulated femoral artery by means of a Statham P23dB pressure transducer. Cardiac output is determined by the method of thermal dilution using a flow-directed balloon catheter containing a thermistor near its distal tip (Swan-Ganz thermal dilution catheter). The distal tip of the balloon catheter is advanced until it is in a wedge position in the pulmonary artery. The electrical signal from the thermistor is delivered to a Columbus Instrument Cardiac Output Computer (Columbus is a Registered Trade Mark). The proximal port of the flow-directed catheter is located in the right atrium. Cardiac outputs are obtained by rapidly injecting 2.0 ml of room temperature 0.9 percent sodium chloride solution into the right atrium. Each determination of cardiac output is the mean of three separate measurements. After obtaining satisfactory baseline recordings, test compound is infused *via* the jugular vein at a rate of 5 mg/min. Measurement of the various hemo-dynamic parameters are taken when cumulative doses of 1.0; 5.0 and 10.0 mg/kg has been administered to each of the animals.

All data are expressed as the mean ± S.E. and are analyzed by the method of paired analysis.

ISOLATED PAPILLARY MUSCLES: Right ventricular papillary muscles are removed rapidly from cats (3.7 to 5.2 kg) anesthetized with pentobarbital sodium, 30 mg/kg intraperitoneally and are suspended in a 50 ml organ bath. The lower nontendinous end of the muscle are held by a spring-loaded Lucite (Registered Trade Mark) clip fixed to a rigid stainless steel rod. The upper tendinous end of the muscle is tied with a short length of 4—0 braided surgical silk which is connected to a calibrated Grass FT—03 force displacement transducer. The muscles are stimulated electrically through punctate electrodes at a frequency of 30/minute, with square wave stimuli of 1.0 msec duration and a voltage 10 percent greater than threshold. The muscle baths are filled with a solution of the following compositions, expressed as mM/liter: Na^+, 143; Ca^{++}, 2.5; K^+, 5.9; Mg^{++}, 1.19; Cl^-, 126; HCO^-_3, 25.4; $HPO_4^=$, 1.19; and Dextrose 5 mM and adjusted to a pH of 7.4. The solution is maintained at a temperature of 32.5°C. and is bubbled with 95 percent O_2 and 5 percent CO_2.

Each muscle is stretched to the peak of its length-active tension curve and allowed to stabilize for a period of 2 hours before being exposed to increasing concentrations of test compound. The data are expressed as a percent of initial control force per mm^2 of cross sectional area and analyzed by paired analysis. The electrical signal from the force-displacement transducer is differentiated electronically to obtain the rate of force development, dF/dt, expressed as $gm/sec/mm^2$.

OUABAIN-INDUCED ARRHYTHMIAS IN THE ANESTETIZED DOG: Male, mongrel dogs (8.0 to 13.5 kg) are anesthetized with intravenous pentobarbital sodium, 30 mg/kg. Blood pressure is measured from the femoral artery with a Statham pressure transducer. All drugs are administered into the cannulated left external jugular vein. The right vagus nerve is sectioned and its distal end is stimulated with 1.0 msec square-wave stimuli at a frequency of 40 Hz at 6.0 to 8.0 V.

Ventricular tachycardia is induced by the administration of ouabain, 40 μg/kg, i.v., followed in 30 minutes by 20 μg/kg and every 15 minutes thereafter by an additional 10 μg/kg until ventricular tachycardia develops.

The criteria used to determine antiarrhthymic activity are: 1) reversion to normal sinus rhythm for a period of not less than 30 minutes; 2) failure of stimulation of the distal right vagus nerve to expose automatic ectopic ventricular activity during the period of vagal-induced sinoatrial arrest; and 3) return of the abnormal rhythm after the intravenous administration of insulin, 80 U, to insure the continued presence of ouabain in concentrations sufficient to induce cardiotoxicity. Lead II electrocardiograms are monitored continuously on an oscilloscope and all recordings are made on a Grass model 7 polygraph.

VENTRICULAR ARRHYTHMIAS AFTER CORONARY ARTERY LIGATION:

ONE-STEP LIGATION: Dogs (8.6 to 16.4 kg) are anesthetized with pentobarbital sodium, 30 mg/kg, i.v. and respired by means of Harvard respirator. The heart is exposed through the 5th left intercostal space. The pericardium is opened and tied to the chest wall to form a cradle which supports the heart. The left anterior descending coronary artery is dissected free at a point near its origin. A silk suture is passed under the vessel and the free ends are passed through a short section of polyethylene tubing. The artery can be occluded by pressing the tubing onto the vessel while at the same time pulling up on the free ends of the suture. The occlusion can be terminated and blood reinstituted by releasing the suture and pulling the tubing away from the vessel. In these experiments, acute occlusion of the anterior descending coronary artery is maintained for a period of 20 minutes after which the occlusion is released.

Two groups of animals are studies: controls, which receive a saline infusion; and animals treated with test compound in a dose of 10 mg/kg, i.v. The Lead II electrocardiogram and femoral arterial pressure are recorded on magnetic tape (Harvard Physiological Tape Recorder) for subsequent analysis and recording on a Grass model 7 polygraph).

TWO - STEP LIGATION: Mongrel dogs (10.8 to 12.8 kg) are anesthetized with intravenous pentobarbital sodium, 30 mg/kg and placed on positive pressure ventilation with room air *via* a cuffed endotracheal tube. Under aseptic conditions, a thoractomy is performed in the 5th, left intercostal space and a 5 to 8 mm segment of the left anterior descending coronary artery is dissected free at a point just below the border of the left atrial appendage. A double ligature is passed under the artery and the vessel is occluded in two stages according to the method described by Harris, *Circulation, 1,* 1318 (1950). Sterile catheters (0.040 in I.D.) are placed in the external jugular vein and the left carotid artery. These are exteriorized *via* a small stab wound at the back of the neck and are maintained patent by periodic flushing with sterile heparin solution. The animals are studied at 24 and 48 hours later in the unanesthetized state. The Lead II electrocardiogram and arterial blood pressure are continuously recorded while the animals are supported in a harness and maintained in a quiet environment. Test compound is administered at a constant infusion rate of 5 mg/min *via* the jugular vein catheter. The electrocardiographic recordings are analyzed according to the method of Moran *et al.* (1962), in which only beats of sinoatrial origin are considered as normal and all other QRS complexes are classified as ectopic.

DETERMINATION OF VENTRICULAR FIBRILLATION THRESHOLD: These experiments are performed on mongrel dogs (10.2 to 11.6 kg) anesthetized with pentobarbital sodium, 30 mg/kg, i.v. The animals are maintained by positive pressure respiration by a Harvard respirator pump. The heart is exposed through a thoracotomy in the 5th intercostal space and suspended in a pericardial cradle. The Lead II electrocardiogram is monitored continuously on an oscilloscope.

Double bipolar silver-silver chloride electrodes, embedded in an acrylic plaque, are sutured to the surface of the right ventricle. One pair of electrodes delivers the basic pacing stimulus while the second pair of electrodes delivers a gated train of impulses. The sinoatrial node is crushed, and the heart rate is maintained by electrically pacing the ventricle at a rate of 2 cps. The ventricular fibrillation threshold is determined by delivering a train of impulses during the ventricular vulnerable period, starting 50 msec after ventricular activation and lasting 250 msec. The train of impulses, 60 Hz, 2 msec duration, is synchronized to the ventricular pacing stimulus and is delivered 50 msec after every sixth basic driven beat. The current delivered is measured directly on an oscilloscope by recording the series with the electrodes. The current intenvoltage drop across a 100 ohm resistor in sity is increased by increments of 0.5 mA until ventricular fibrillation develops. The ventricular fibrillation threshold is defined as the minimum current in milliamperes (mA) of the test pulse which induce ventricular fibrillation. When fibrillation ensues, the heart is immediately defibrillated using a capacitor DC defibrillator (Physio-Control series 70). Thresholds are determined before and after administration of test compound, 10 mg/kg. Results are compared using Student's t-test for paired comparisons.

The novel composition of this invention consist of one of the aforementioned active ingredients combined with a pharmaceutically acceptable carrier. These compositions can be administered either orally or parenterally. For oral administration tablets, lozenges, capsules, dragees, pills or powders are suitable, while aqueous solutions, non-aqueous solutions or suspensions are appropriate for parenteral administration. Acceptable pharmaceutical carriers are exemplified by gelatin capsules, sugars such as lactose or sucrose, starches such as corn starch or potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose or cellulose acetate phthalate, gelatin, talc, calcium phosphate such as dicalcium phosphite or tricalcium phosphate, sodium sulfate, calcium sulfate, polyvinylpyrrolidone, acacia, polyvinyl

alcohol, stearic acid, alkaline earth metal stearates such as magnesium stearate, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil or theobroma, water, agar, alginic acid, benzyl alcohol, isotonic saline and phosphate buffer solutions as well as other non-toxic compatible substances.

The compositions of the present invention can be used also in combination with other known pharmaceutical agents. For example, they can be used together with known anti-anginal agents such as the long-acting nitrites. They can, furthermore, be utilized in combination with other known anti-arrhythmic agents such as quinidine. In addition, they can be used in combination with known hypotensile agents.

The invention will appear more fully from the examples which follow. They are not to be construed as limiting the invention in scope as variations both in materials and in methods will be apparent to those skilled in the art. In the following examples, temperatures are given in degrees Centigrade (°C) and quantity of materials in parts by weight unless parts by volume is specified.

EXAMPLE 1.

34.0 grams (0.20 moles) of 2-phenylphenol and 10.2 grams (0.25 moles) of sodium hydroxide were dissolved in 250 ml of water. The reaction mixture was cooled in ice and 25.0 g (2.27 moles) of epichlorohydrin was added slowly with stirring. Stirring was continued at room temperature for about 42 hours. Then the mixture was extracted with chloroform and the chloroform extracts were washed with water until neutral. The chloroform extract was dried over anhydrous potassium carbonate and the solvent evaporated under reduced pressure. There was afforded thereby 2,3 - epoxy - 1 - (2 - phenylphenoxy)-propane as a blue-green oil.

EXAMPLE 2.

Substitution of an equivalent quantity of 3-phenylphenol in the procedure of Example 1 afforded 2,3 - epoxy - (3 - phenylphenoxy)-propane as an amber oil.

EXAMPLE 3.

Substitution of an equivalent quantity of 4-phenylphenol and replacing sodium hydroxide by potassium hydroxide in the procedure of Example 1, afforded 2,3 - epoxy - 1 - (4-phenylphenoxy)propane as a white solid melting at about 112—116°C.

EXAMPLE 4.

22.7 g (0.1 mole) of 2,3 - epoxy - 1 - (2-phenylphenoxy)propane was dissolved in 30 ml of methanol. Then 15 ml (0.2 moles) methylisopropylamine was added to the reaction mixture slowly while stirring. The mixture was refluxed over a steam bath for 48 hours after which time the solvent and excess amine were evaporated under reduced pressure. The residue remaining was dissolved in 200 ml of ether and the solution was washed with water. The ether phase was extracted with 5% aqueous hydrochloric acid and the aqueous extracts were washed once with ether. The aqueous phase was neutralized with ammonium hydroxide, then extracted with methylene chloride. The methylene chloride extract were dried over anhydrous potassium carbonate and the solvent evaporated under reduced pressure to afford 1 - (N-isopropyl - N - methylamino) - 3 - (2-phenylphenoxy) - propan - 2 - ol, as a blue-green oil.

EXAMPLE 5.

When an equivalent quantity of 2,3 - epoxy-1 - (3 - phenylphenoxy)propane was substituted in the procedure of Example 4, there was obtained, as an amber oil, 1 - (N - isopropyl - N - methylamino) - 3 - (3 - phenylphenoxy)propan - 2 - ol.

EXAMPLE 6.

By substituting an equivalent quantity of 2,3 - epoxy - 1 - (4 - phenylphenoxy)-propane and 30 ml of a 1:1 methanol-chloroform solution in the procedure of Example 4, there was afforded 1 - (N - isopropyl-N - methylamino) - 3 - (4 - phenylphenoxy)-propan - 2 - ol.

EXAMPLE 7.

To a solution of 10.0 g (0.033 moles) of 1 - (N - isopropyl - N - methylamino) - 3-(2 - phenylphenoxy)propan 2 - ol and 30 ml of acetone, placed in a pressure container cooled in a Dry Ice-acetone bath was added 30 ml of methyl chloride. The container was sealed and mixture stirred at room temperature for about 8 days, after which time the mixture was again cooled in a Dry Ice-acetone bath. The container was opened slowly to permit reduction of any excess pressure and the solvent and excess methyl chloride was removed by evaporation under reduced pressure. The material remaining was dissolved in 30 ml of absolute ethanol, which then was evaporated under reduced pressure. The latter procedure was repeated and the residue was crystallized from anhydrous acetone to afford [3 - (2 - phenylphenoxy) - 2 - hydroxypropyl]isopropyldimethylammonium chloride melting at about 124—127°C.

EXAMPLE 8.

Substitution of an equivalent quantity of 1 - (N - isopropyl - N - methylamino) - 3-(3 - phenylphenoxy)propan - 2 - ol in the procedure of Example 7 yielded [3 - (3-

phenylphenoxy) - 2 - hydroxypropyl]isopropyldimethylammonium chloride, melting at about 254—256°C.

EXAMPLE 9.

By substituting an equivalent quantity of 1 - (N - isopropyl - N - methylamino) - 3-(4 - phenylphenoxy)propan - 2 - ol in the procedure of Example 7, there was obtained [3 - (4 - phenylphenoxy) - 2 - hydroxy]-propyl]isopropyldimethylammonium chloride, melting at about 254—256.5°C.

EXAMPLE 10.

By substituting an equivalent quantity of dimethylamine in place of the methylisopropylamine utilized in Example 4 and subsequently following the procedures of Example 4 and Example 7, there was produced [3 - (2-phenylphenoxy) - 2 - hydropropyl]trimethylammonium chloride.

EXAMPLE 11.

Substitution of an equivalent quantity of ethylisopropylamine for the methylisopropylamine utilized in Example 4 and subsequently following the procedures outlined in Example 4 and Example 7 afforded [3 - (2 - phenylphenoxy) - 2 - hydroxypropyl]ethylisopropylmethylammonium chloride.

EXAMPLE 12.

Substitution of an equivalent quantity of methyl iodide in the procedure of Example 7 afforded [3 - (2 - phenylphenoxy)-2 - hydroxypropyl]isopropyldimethylammonium iodide.

Pharmaceutical formulations of special value are tablets, capsules, suppositories and packaged solutions for parenteral administration, in particular solutions packed in ampoules.

In the preparation of tablets and capsules from the compounds of the present invention, a variety of excipients can be used. There are summarized as follows: Sugars such as lactose, sucrose, mannitol, or sorbitol; starches such as corn starch, tapioca starch, or potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, or methyl cellulose; gelatin, calcium phosphates such as dicalcium phosphate or tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates such as magnesium stearate; stearic acid, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil; surfactants nonionic, cationic, anionic); ethylene glycol polymers; beta-cyclodextrin; fatty alcohols; hydrolyzed cereal solids; as well as other nontoxic compatible fillers, binders, disintegrants and lubricants commonly used in pharmaceutical formulations.

In the preparation of parenteral products from the compounds of the present invention a variety of vehicles and solubilizers can be used. These are summarized as follows: Vegetable oils such as peanut, corn, cottonseed, sesame oil, benzyl alcohol, saline, phosphate buffer, water, ethylene glycol polymers, urea, dimethylacetamide, "Triton" (Triton is a Registered Trade Mark), dioxolanes, ethyl carbonate, ethyl lactate, glycerol formal, isopropyl myristate, surfactants (nonionic, cationic, anionic) polyalcohols, ethanol.

In the preparation of suppositories from the compounds of the present invention a variety of vehicles and bases for suppository application can be used. These are summarized as follows: Triglycerides of oleic, palmitic, and stearic acids (cocoa butter), partially hydrogenated cottonseed oil, branched saturated fatty alcohols such as Suppository base G, Hydrogenated coconut oil triglycerides of C_{12}—C_{18} fatty acids, water dispersible vehicles such as the polyethylene glycols, glycerin, gelatin, polyoxyl 40 stearates, and polyethylene - 4 - sorbitan monostearates, and materials which can raise the melting point of the suppository base, such as beeswax, spermaceti, etc.

The following Examples illustrate pharmaceutical compositions containing the compounds of this invention. In each example, the quantities of materials specified were utilized to produce 1000 dosage units in the indicated form.

EXAMPLE 13.

175 Grams of [3 - (2 - phenylphenoxy)-2 - hydroxypropyl]isopropyldimethyl ammonium chloride were dissolved in isopropyl alcohol and distributed on 131 grams of lactone. The mixture was air-dried and passed through a 40 mesh screen. 80 Grams of corn starch and 12 grams of polyvinylpyrrolidone were added to and mixed thoroughly with the mixture which had passed through the screen and the mixture which had passed through the screen and the mixture which was formed was passed through a 40 mesh screen. The mixture was then granulated with isopropyl alcohol, spread on trays, and dried at 120°F. for 16 hours. The dried granulation product was then screened. The granules were mixed thoroughly with 2.0 grams of magnesium stearate and the mixture compressed into tablets of the appropriate size. There was thus obtained a batch of 1000 tablets each containing 175 mg of active ingredient per tablet.

EXAMPLE 14.

175 Grams of [3 - (2 - phenylphenoxy)-2 - hydroxypropyl]isopropyldimethylammonium chloride were mixed thoroughly with 92.5 grams of corn starch and 92.5 grams of

lactose, screened through a 40 mesh screen, and remixed. 40 Grams of talc were added and the mixture was thoroughly mixed and employed to fill hard gelatin capsules in an amount of 400 mg. mixture per capsule. There was thus obtained a batch of 1000 capsules each containing 175 mg active ingredient per capsule.

EXAMPLE 15.

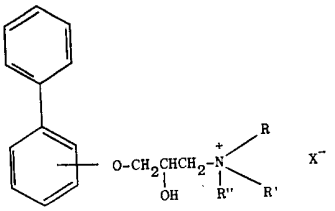
250 Grams of [3 - (2 - phenylphenoxy)-2 - hydroxypropyl]isopropyl dimethylammonium chloride were dissolved in 5.0 liters of water. The solution obtained was filtered and used to fill ampuls which were then sealed. The ampuls were then sterilized. There was thus obtained a batch of 1000 ampuls each containing 5 ml of solution containing 250 mg of active ingredient.

EXAMPLE 16.

825 Grams of cocoa butter were melted on a steam bath to avoid local overheating. 175 grams of [3 - (2 - phenylphenoxy) - 2-hydroxypropyl] - isopropyl dimethylammonium chloride were then emulsified in the melt. The mass obtained was then poured into cooled metal molds, which were chrome plated and in which suppositories readily solidified. The total weight of each suppository was 1 gram. That is each suppository contained 175 mg. of active ingredient.

WHAT WE CLAIM IS:—

1. A compound of the formula:—



(I)

wherein R, R′ and R″ which can be the same or different are alkyl groups containing from 1 to 4 carbon atoms and X^- is the anion of a pharmacologically acceptable non-toxic acid.

2. A compound as claimed in Claim 1, wherein R and R′ are methyl and R″ is isopropyl.

3. A compound as claimed in Claim 1, wherein R and R′ are methyl, R″ is isopropyl, X is halide and the phenylphenoxy group is 2-phenylphenoxy.

4. A compound as claimed in Claim 1, 2 or 3, wherein X^- is chloride, iodide, bromide, fluoride, sulphate, C_{1-4}-, alkylsulphate or ortho-, metal- or pyrophosphate.

5. [3 - (2 - Phenylphenoxy) - 2 - hydroxypropyl]isopropyldimethylammonium chloride.

6. [3 - (3 - Phenylphenoxy) - 2 - hydroxypropyl]isopropyldimethylammonium chloride.

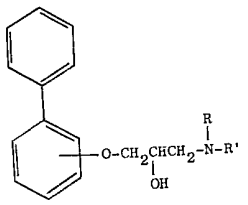
7. [3 - (4 - Phenylphenoxy) - 2 - hydroxypropyl]isopropyldimethylammonium chloride.

8. [3 - 2 - Phenylphenoxy - 2 - hydroxypropyl]trimethylammonium crloride.

9. [3 - (2 - Phenylphenoxy) - 2-hydroxypropyl] ethylisopropylmethylammonium chloride.

10. [3 - (2 - Phenylphenoxy) - 2-hydroxypropyl] isopropyldimethylammonium iodide.

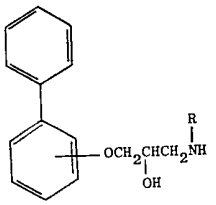
11. A process for the preparation of a compound as claimed in Claim 1, wherein X^- is halide, which comprises reacting a compound of the of the formula:



(II)

wherein R and R′ are alkyl radicals containing from 1 to 4 carbon atoms with a compound of the formula R″X wherein R″ is an alkyl radical containing from 1 to 4 carbon atoms and X is halide.

12. A process for the preparation of a compound as claimed in Claim 1 wherein X^- is halide, which comprises reacting a secondary amine of the formula:



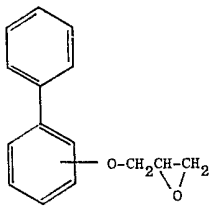
(III)

wherein R is an alkyl group containing from 1 to 4 carbon atoms with two molar equivalents of a compound of formula R″X wherein R″ is an alkyl group containing from 1 to 4 carbon atoms and X is halide.

13. A process as claimed in Claim 11 or 12, wherein to produce a compound wherein X^- is an anion other than halide, the halide ions of the compound which is produced are replaced by said other ions in an ion exchange procedure.

14. A process as claimed in claim 11 or 12, wherein the compound of formula R″X is methyl chloride or methyl iodide.

15. A process as claimed in any one of Claims 11, 12, 13 or 14, wherein the compound of formula II or III is the product of reaction (2, 3, or 4) - phenylphenol with epichlorohydrin in the presence of an aqueous alkali to yield a compound of formula:



(IV)

which is then refluxed with a primary or secondary alkyl amine to yield a compound of formula II or III respectively.

16. A process for the production of a compound as claimed in Claim 1, substantially as described in any one of the foregoing Examples 7 to 12.

17. A pharmaceutical composition which comprises a compound as claimed in any one of Claims 1 to 9, in association with a pharmacologically acceptable carrier.

18. A composition as claimed in Claim 17, which is in the form of a tablet, capsule, a packaged solution for parenteral administration, or suppository.

19. A composition as claimed in Claim 17 or 18, which is in dosage unit form, each dosage unit containing from 175 to 250 mg of a said compound.

20. A composition as claimed in any one of Claims 17 to 19, which additionally contains an anti-anginal agent.

21. A composition as claimed in Claim 20 in which the anti-anginal agent is a long acting nitrite.

22. A composition as claimed in any one of Claims 17 to 21, which additionally contains quinidine.

23. A composition as claimed in any one of Claims 17 to 22, which additionally contains a hypotensive agent.

24. A pharmaceutical compoosition, substantially as described in any one of the foregoing Examples 13 to 16.

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