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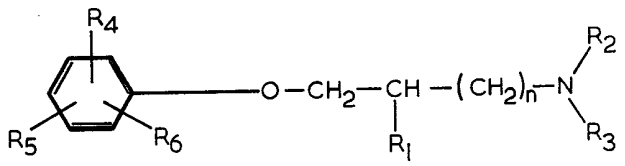
(19)

(54) IMPROVEMENTS IN OR RELATING TO TERPENOPHENOXYALKYLAMINES

(71) We, MAR-PHA, Societe d'Etude et d'Exploitation de Marques, a Societe anonyme organised under the laws of France, of 25 Boulevard de L'Amiral Bruix, 75116 Paris, France, do hereby declare the invention for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

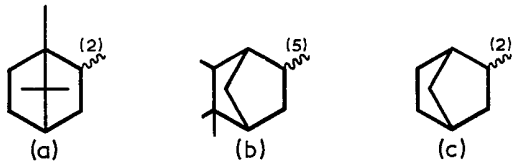
The invention described in the main patent relates to terpenophenoxyalkylamines of the general formula:



(I)

in which n=0 or 1

R_1 is a hydrogen atom when n is 0 or R_1 is an OH group when n is 1, R_2 and R_3 are the same or different and represent H or a lower alkyl radical having a straight or branched chain with up to 4 carbon atoms, or a hydroxyethyl radical, with the proviso that when n is 0 R_2 is H and R_3 is H or a hydroxyethyl radical, R_4 is a terpene radical: 2-exoisobornyl (a), or 5-isocamphyl (b), or 2-norbornyl (c),



the 5-isocamphyl group and 2-norbornyl group being of exo or endo configuration, and said terpene radical being in the ortho, meta or para position with respect to the ether function;

R_5 and R_6 are the same or different and represent H or a lower alkyl radical having up to 4 carbon atoms and having a straight or branched chain, or a halogen atom:

Cl, Br, I, F.

Preferably:

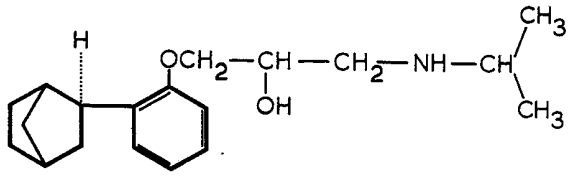
— R_2 is a hydrogen atom,

— R_3 is a hydrogen atom, an isopropyl radical or a hydroxyethyl group (i.e. $—CH_2CH_2—OH$),

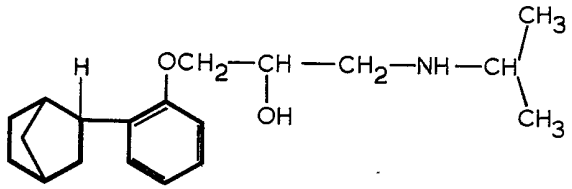
— R_5, R_6, are the same or different and represent a hydrogen atom or a halogen atom, in particular Cl, or Br, or a methyl radical, in position 4 or 5 of the phenol ring.

In particular, these amino-ethers have interesting bacteriostatic and bactericidal properties as regards gram + germs and gram — germs and can be used as anti-infectious agents. They also have vasodilatory and cardiovascular properties. They may be used in the form of physiologically acceptable non-toxic bases or acid addition salts, or in the form of quaternary ammonium salts.

The present addition provides terpenophenoxyalkylamines chosen from the group comprising 1-isopropylamino-3-[2-(2-*exo*-norbornyl) phenoxy]propan-2-ol of the formula:



and 1-isopropylamino-3-[2-(2-*endo*-norbornyl)phenoxy]propan-2-ol of formula:



as well as their physiologically acceptable non-toxic acid addition salts, in particular their hydrochlorides. The invention also provides a pharmaceutical composition comprising, as an active ingredient at least one of the compounds of the invention associated in a physiologically active quantity with a non-toxic pharmaceutically acceptable carrier.

It is quite unexpected that in addition to the aforementioned properties for terpenophenoxyalkylamine compounds, these isomers have a beta-blocking or beta-sympatholytic activity over a prolonged period of time.

These new amino-ethers may be prepared by condensation of an alkali metal 2-(2-*exo*- or *endo*-norbornyl) phenate with an epihalohydrin, preferably epichlorohydrin, to form the 1-[2-(2-*exo*- or *endo*-norbornyl)phenoxy]-2,3-epoxypropane and reaction of the latter with isopropylamine, according to the general method described in the main patent.

The invention is illustrated by the following non-limiting examples:

EXAMPLE 1

1-isopropylamino-3-[2-(2-*exo*-norbornyl)phenoxy]-propan-2-ol

— 24.5g (0.13 mole) 2-(2-*exo*-norbornyl) phenol (L.A. KHEIFITS and A.E. GOL'DOVSKII, Zh. Obshch. Khim., 1936, *33*, 2048.), 350 cm^3 anhydrous toluene and 3g (0.13 mole) metallic sodium are introduced into a three-neck flask through which a stream of nitrogen flows.

— The reaction mixture is refluxed until the liberation of hydrogen ceases, then the solvent is driven off under reduced pressure and the residue is taken up in 250 cm^3 tetrahydrofuran. 24g (0.26 mole) epichlorohydrin are then added and the mixture is heated under reflux for 6 hours. An extraction with ether is then undertaken, the organic phase is washed with water, dried and the solvent is evaporated. 25g 1-[2-(2-*exo*-norbornyl)phenoxy]-2,3-epoxypropane are thus obtained in the form of an oil.

— 15g (0.06 mole) of the preceding product are dissolved in 50 cm_n isopropylamine. After 4 days contact, the excess amine is evaporated under reduced pressure, then an extraction with ether is carried out. After washing with water and drying, the ethereal phase is saturated with gaseous hydrochloric acid.

— The precipitate formed is washed abundantly with ether then crystallised from an acetone/ethanol mixture (3/2). 16g of the desired product in the form of the hydrochloride are thus obtained, having a melting point of 189—191°C.

Analytical Characteristics

Analysis for $C_{19}H_{30}ClNO_2$ (molecular weight 339)

	C%	H%	N%
Calculated	67.25	8.84	4.12
Found	67.20	8.82	3.83

Infrared Spectrum

In dispersion in KBr, the characteristic bands are as follows:

$\overset{\oplus}{—NH_2}$ 2795 cm^{-1}, 1585 cm^{-1}

—OH 3300 cm^{-1}

— aromatic ring 1600, 1500, 750 cm^{-1}

— ether linkage 1245 cm^{-1}, 1045 cm^{-1}

Nuclear Magnetic resonance

In solution in D.M.S.O. d_6 (deuterated dimethylsulphoxide), the following are noted with respect to H.M.D.S.

— Norbornyl 1.3 ppm

— Isopropyl methyls 1.2 ppm (doublet)

— Methine 4.2 ppm

— Aromatic protons 6.9 ppm.

EXAMPLE 2

1-isopropylamino-3-[2-(2-*endo*-norbornyl)phenoxy]propan-2-ol

200 cm^3 anhydrous toluene and 3.45g (0.15 mole) metallic sodium are introduced into a 1 litre three-neck flask, through which a stream of nitrogen flows. The mixture is heated under reflux, with vigorous stirring, then 28.24g (0.15 mole) 2-(2-*endo*-norbornyl)phenol (L.A. KHEIFITS, A.E. GOL'DOVSKII J. Org. Chem. U.S.S.R. 1969, *5* (10), 1745—1748) are then added slowly. At the end of this addition, heat is applied for 1 hour, then the solvent is driven off under reduced pressure and the residue is taken up in 200 cm^3 tetrahydrofuran. 27.75g (0.3 mole) epichlorohydrin are then added and one heats under reflux for 3 hours. The solvent is eliminated by evaporation and the residue is taken up in ether, the insoluble material is filtered over "Celite" (Registered Trade Mark) and the organic phase is washed abundantly with water. The ethereal layer is dried and the ether is eliminated by evaporation in order to obtain 32g 1-[2-(2-*endo*-norbornyl)phenoxyl]-2,3-epoxypropane, in the form of an oil.

15g (0.06 mole) of the latter product are then dissolved in 50 cm^3 isopropylamine and the resulting solution is left for 3 days at ambient temperature. The excess amine is evaporated under reduced pressure, then an extraction with ether is carried out. The ethereal phase after washing with water and drying, is then saturated with gaseous hydrochloric acid. The precipitate thus formed, crystallised from acetone, gives 9.3g of the desired product, in the form of the hydrochloride having a melting point of 162—164°C.

Analytical Characteristics

Analysis for $C_{19}H_{30}ClNO_2$ (molecular weight 339)

	C%	H%	N%
Calculated	67.25	8.84	4.12
Found	67.26	8.84	3.93

Infrared Spectrum

In dispersion in KBr the characteristic bands are as follows:

$-\overset{\oplus}{N}H_2$ 2795 cm^{-1}, 1560 cm^{-1}

—OH 3300 cm^{-1}

— aromatic ring 1600, 1500, 755 cm^{-1}

— ether linkage 1250 cm^{-1}, 1060 cm^{-1}

Nuclear Magnetic Resonance

In solution in deuterated chloroform, the following are noted with respect to TMS

— norbornyl 1.3 ppm

— isopropyl methyls 1.45 ppm (doublet)

— methine 4.6 ppm

— aromatic protons 7 ppm.

TOXICOLOGICAL PROPERTIES

Acute toxicities of the compounds according to the invention have been determined in the male mouse CD1 (Charles RIVER) both intravenously and orally. The LD50 were calculated after observation for 3 days by the method of REED, JJ. and MUENCH, H. (Am. J. Hy, *27* 493, 1938).

The LD50 obtained are summarised in the following table:

No. of Example	Acute toxicity in the mouse LD50 mg/kg	
	Intravenously	Orally
1	60	800
2	62	675

The two compounds behave as substances which are only relatively slightly toxic in the mouse.

PHARMACOLOGICAL PROPERTIES

1. beta-sympatholytic properties

The beta-sympatholytic properties of the two compounds of the invention

have been demonstrated in a non-anesthetized rabbit intravenously and orally.

The technique consists of evaluating the antagonism exerted by the products with regard to induced tachycardia, in an alert rabbit, by a sympatho-stimulant agent, isoproterenol, administered in a dose of 0.010mg/kg intravenously. The animal is placed in a restraining box and the marginal vein of the ear is catheterized. The animal's electrocardiogram is picked up by two electrodes implanted in shunt DII and connected to a telemetric transmitter. A polygraph, coupled to a receiver, simultaneously records the electrocardiogram and the cardiac rhythm by integration of the waves R.

First of all, one makes certain of the stability and reproducibility of isoprenalinic tachycardia and the substance to be studied is administered. In the case of intravenous administration of the products, the injections of isoproterenol are then repeated 5 minutes later, then every 15 minutes, until the tachycardia returns to its initial intensity. When the products are administered orally, the injections of the beta-stimulant are repeated 15, 30, 45 and 60 minutes, then 2, 3, 5, 24 and 48 hours afterwards.

The beta-sympatholytic activity is expressed by the maximum percentage decrease of the tachycardia induced by iso-proterenol. The total duration of the effect is also noted.

The following tables summarise the results obtained with the products according to the invention:

A – Intravenous administration

Example	Intravenous dose mg/kg	Maximum Inhibition of tachycardia (as a %)	Duration of Inhibiting effect
1	0.1	24	approx. 50 minutes
	0.3	67	approx. 2½ hours
	0.5	54	more than 2 hrs.
	1	86	more than 2 hrs.
2	0.5	20	approx. 40 mins.
	1	67	approx. 4 hrs.

B – Oral Administration

Example	Oral dose mg/kg	Maximum Inhibition of tachycardia (as a %)	Duration of Inhibiting effect
1	9	40	more than 3 hrs.
	17.5	73	approx. 24 hrs.
	35	88	approx. 48 hrs.
	75	80	approx. 48 hrs.
	150	82	more than 48 hrs.
2	17.5	64	approx. 24 hrs.
	35	60	approx. 48 hrs.
	75	80	approx. 48 hrs.
	150	81	approx. 48 hrs.

The two products of the invention therefore exert powerful beta-sympatholytic effects, which last for a surprisingly long time when administered both intravenously as well as orally.

2. Coronaro-dilatory activities

The coronaro-dilatory activities of the compounds of the invention have been demonstrated on a rabbit's heart in a technique derived from that of LANGENDORFF, (Arch. Ges. Physiol., *61*, 201, 1895). In this technique, the survival liquid perfusing the heart contains 0.5 I.U./l post-hypophysis intended for permanently maintaining a slight vaso-constriction of the coronary vascular system. The products to be studied are administered in the region of the aortic canal in a volume of 1 cm^3 over a period of 1 minute. The results are expressed as a percentage variation of the coronary output after the injection of the product with respect to the initial output, the output being measured by integration of the

frequency of drops of survival liquid escaping from the heart after having passed through the coronary system.

The results obtained with the product of Example 1 are given in the following table:

Dose in mg/l	% Variation of coronary output	Duration of the effect in mins
0.003	+ 13	3
0.010	+ 57	3
0.030	+ 133	15
0.100	+ 225	9

The product of Example 1 exerts considerable coronaro-dilatory effects, whose intensity and duration clearly increase with the concentration.

3. Spasmolytic activity

The spasmolytic activities of the compounds of the invention have been demonstrated by means of the technique of MAGNUS R. (Arch. Ges. Physiol., *102*, 123, 1904) on the removed duodenum of the rat. The spasmolytic neurotropes inhibit the contractions of the organ caused by acetylcholine, whereas the musculotropes prevent the spasms induced by barium chloride. The following table summarises the results expressed as a 50% effective concentration (EC50) in mg/l.

Example	Spasmolytic activities on the detached duodenum of the rat (EC50) mg/l	
	Neurotrope (versus-acetylcholine)	Musculotrope (versus-$BaCl_2$)
1	0.18	0.15
2	0.30	0.04

The two products of the invention have powerful spasmolytic properties, both neurotropic and musculotropic.

THERAPEUTIC USE

In view of their considerable and lasting beta-adrenolytic activities, associated with vasodilatory and spasmolytic properties, the products of the invention may be used to treat humans in all fields of application of beta-sympatholytic substances, in particular against various disorders of the cardiac rhythm and as anti-anxiety and anti-hypertension substances for example. They may also be used as anti-spasmodic substances.

The compounds according to the invention and their pharmaceutically acceptable salts may be administered in the form of tablets, sugar coated pills, capsules, cachets, suppositories, injectable ampoules, drinkable liquids etc. in unitary doses comprised, according to the galenic forms and compounds, between 10 and 200 mg according to a daily dosage which can vary from 20 to 1200mg.

WHAT WE CLAIM IS:—

1. 1-Isopropylamino-3-[2-(2-exo-norbornyl)phenoxy]propan-2-ol, and its physiologically acceptable non-toxic acid addition salts.

2. 1-Isopropylamino-3-[2-(2-endo-norbornyl)-phenoxy]propan-2-ol, and its

physiologically acceptable non-toxic acid addition salts.

3. Pharmaceutical composition comprising, as an active ingredient, at least one compound according to claim 1 or 2, associated in a physiologically active quantity with a non-toxic pharmaceutically acceptable carrier.

4. Pharmaceutical composition according to claim 3, produced in the form of a tablet, sugar coated pill, capsule, cachet, suppository, injectable ampoule, or drinkable liquids, in unitary doses of between 10 and 200 mg.

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