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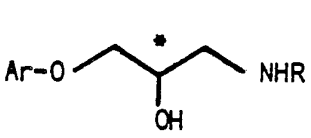

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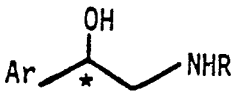

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(57) Abstract

A process for preparing a racemic or chiral aryloxypropanolamine (1) or arylethanolamine (2) of formula (1) or (2), wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, substituted alkyl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $-NR_2COR_3$, $-NR_2CONR_3R_4$, $-NR_2SO_2R_3$, $-NR_2SO_2NR_3R_4$, or $-NR_2COOR_5$, where R_2, R_3, R_4, and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $-NR_2SO_2R_3$ or $-NR_2COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group. The process can be used to prepare beta-blocking agents, useful in the treatment of cardiac conditions.

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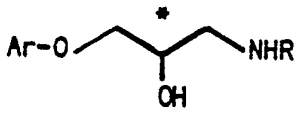
SYNTHESIS OF OPTICALLY ACTIVE ARYLOXYPROPANOLAMINES AND ARYLETHANOLAMINES

BACKGROUND OF THE INVENTION

Aryloxypropanolamines (1) and arylethanolamines (2) are widely used therapeutic agents, particularly those compounds possessing potent beta-adrenergic receptor blocking activity. These beta-adrenergic blocking agents are widely used for a number of cardiovascular therapeutic indications, such as hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction and more recently in the treatment of glaucoma. In addition, certain aryloxypropanolamines possess potent beta-adrenergic stimulating properties and such compounds are used as cardiac stimulants.

Among beta-blocker oxypropanolamines, the R isomers are less active or essentially devoid of beta-blocking activity as compared to their counterpart S isomers. Similarly, the R-isomer beta-agonists are more potent agents than their S-isomer counterparts.



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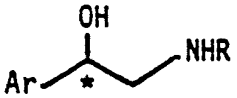
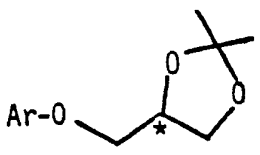


2

Conventional methods for preparing such compounds utilize the hydrolysis of the ketal 3 to give the diol 4 followed by the HBr/AcOH treatment to provide the bromoacetoxy 5. Subsequently, the bromoacetoxy 5 is transformed into an epoxide which is then treated with the corresponding amine to provide the desired beta-blocker in separate stages. Such a procedure is described by S. Iriuchijima and N. Kojima, Agric. Biol. Chem. 46 (5), 1153 (1982). In such a procedure, to prepare the optically active aryloxypropanolamines, four steps are required, starting from the ketal 3. An efficient and an economical process for preparing the separate isomers is therefore highly desirable.



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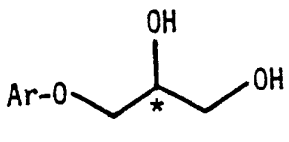

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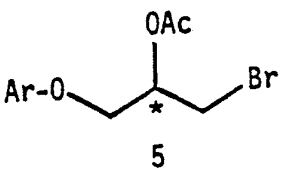

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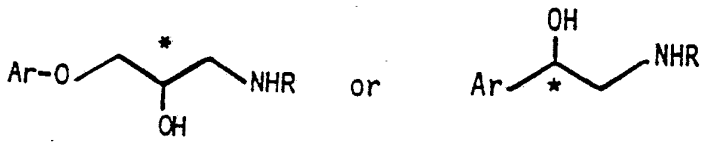
SUMMARY OF THE INVENTION

In accordance with the present invention, disclosed is a process for preparing a racemic or chiral aryloxypropanolamine (1) or arylethanolamine (2) of the formula



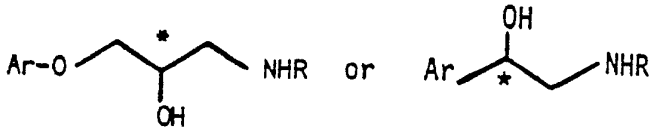
1 2

wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, substituted alkyl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $-NR_2COR_3$, $-NR_2CONR_3R_4$, $-NR_2SO_2R_3$, $-NR_2SO_2NR_3R_4$, or $-NR_2COOR_5$, where R_2, R_3, R_4, and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $-NR_2SO_2R_3$ or $-NR_2COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group.

As an example, a specific embodiment of the method involves the utilization of an HBr/acetic acid (AcOH) mixture to directly convert the ketal 3 to the bromoacetoxy 5 without going through the intermediate diol 4. The bromoacetoxy 5 is then allowed to react with a selected amine in an alcoholic medium to provide the desired aryloxypropanolamine. An alternative procedure for the latter reaction is to convert the bromoacetoxy 5 to an epoxide followed by amination. The method offers the convenience of fewer reaction steps. More generally, a mixture of a strong acid, HX, where X is chloro, bromo or iodo, in an amount of from 0.1 to 50% in an organic acid, Y-COOH where Y is hydrogen, loweralkyl or cycloalkyl, is used to convert the ketal 3.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, disclosed is a process for preparing optically active aryloxypropanolamines (1) or arylethanolamines (2) of the formula



1 2

wherein Ar is aryl, substituted aryl, heteroaryl or aralkyl and R is alkyl, substituted alkyl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B represents $-NR_2COR_3$, $-NR_2CONR_3R_4$, $-NR_2SO_2R_3$, $-NR_2SO_2NR_3R_4$, or $-NR_2COOR_5$ wherein R_2, R_3, R_4 and R_5 may be the same or different and may be hydrogen, alkyl of from 1 to about 10 carbon atoms and preferably from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 10 carbon atoms and preferably from 1 to about 6 carbon atoms; cycloalkyl of from 3 to about 8 carbon atoms, alkenyl of from 3 to about 10 carbon atoms, alkoxyaryl wherein the alkyl group contains from 1 to about 6 carbon atoms, alkynyl of from 3 to about 10 carbon atoms, aryl which includes substituted or unsubstituted monocyclic or polycyclic aromatic or heterocyclic ring systems of from 6 to about 10 carbon atoms such as phenyl, thienyl, imidazole, oxazole, indole, and the like, or aralkyl wherein the alkyl portion contains from 1 to about 6 carbon atoms and the aryl portion represents substituted or unsubstituted monocyclic or polycyclic aromatic or heterocyclic ring systems of from 5 to about 10 carbon atoms such as benzyl, phenethyl, 3,4-dimethoxyphenethyl, 1,1-dimethyl-2-(3-indolyl)ethyl and the like; except that R_3 and R_5 are not hydrogen when B is $-NR_2SO_2R_3$ or $-NR_2COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group such as pyrrolidine, piperidine, piperazine, morpholine, or thiamorpholine.

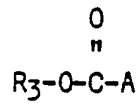
As used herein, the term "aryl" represents a phenyl or naphthyl group which may be unsubstituted or substituted with alkyl of from 1 to about 6 carbon atoms, alkenyl of from 2 to about 6 carbon atoms, alkynyl of from 2 to about 10 carbon atoms, alkoxy wherein the alkyl group contains from 1 to about 6 carbon atoms, halo, acetamido, amino, amido, nitro, alkylamino of from 1 to about 6 carbon atoms, hydroxy, hydroxyalkyl of from 1 to about 6 carbon atoms, cyano or arylalkoxy wherein the alkyl group contains from 1 to about 6 carbon atoms and the aryl group is substituted or unsubstituted phenyl.

The term "heteroaryl" as used herein represents pyridine, pyrazine, pyrrole, pyrazole, piperazine, thiophene, benzothiophene, furan, benzofuran, imidazole, oxazole, indole, carbazole, thiazole, thiadiazole, benzothiadiazole, triazole, tetrazole, azepine, 1, 2-diazepine, or 1,4-thiazepine. Preferably, the heteroaryl is selected from the group consisting of pyridine, pyrazine, thiophene, benzothiophene, benzofuran, indole, carbazole, thiadiazole or benzothiadiazole, with the most preferred being pyrazine, indole, 1,2,5-thiadiazole, or benzofuran.

The term "heterocyclic" as used herein represents pyrrolidine, piperidine, morpholine, or thiamorpholine.

In the term "aralkyl" as used herein, the alkyl group contains from about 1 to about 6 carbon atoms and the aryl group represents substituted or unsubstituted monocyclic or polycyclic aromatic or heterocyclic ring systems of from 5 to about 10 carbon atoms, such as benzyl, phenethyl, 3,4-dimethoxyphenethyl, 1,1-dimethyl-2-(3-indolyl)-ethyl and the like. Aromatic (Ar) substituents may include lower alkyl of from 1 to about 10 carbons atoms, alkenyl of from 2 to about 10 carbon atoms, alkynyl of from 2 to about 10 carbon atoms, alkoxy wherein the alkyl group contains from 1 to about 10 carbon atoms, halo, acetamido, amino, nitro, alkylamino of from 1 to about 10 carbon atoms, hydroxy, hydroxyalkyl of from 1 to about 10 carbon atoms, cyano, arylalkoxy wherein the alkyl group contains from 1 to

about 6 carbon atoms and the aryl group represents substituted or unsubstituted phenyl and groups of the formula

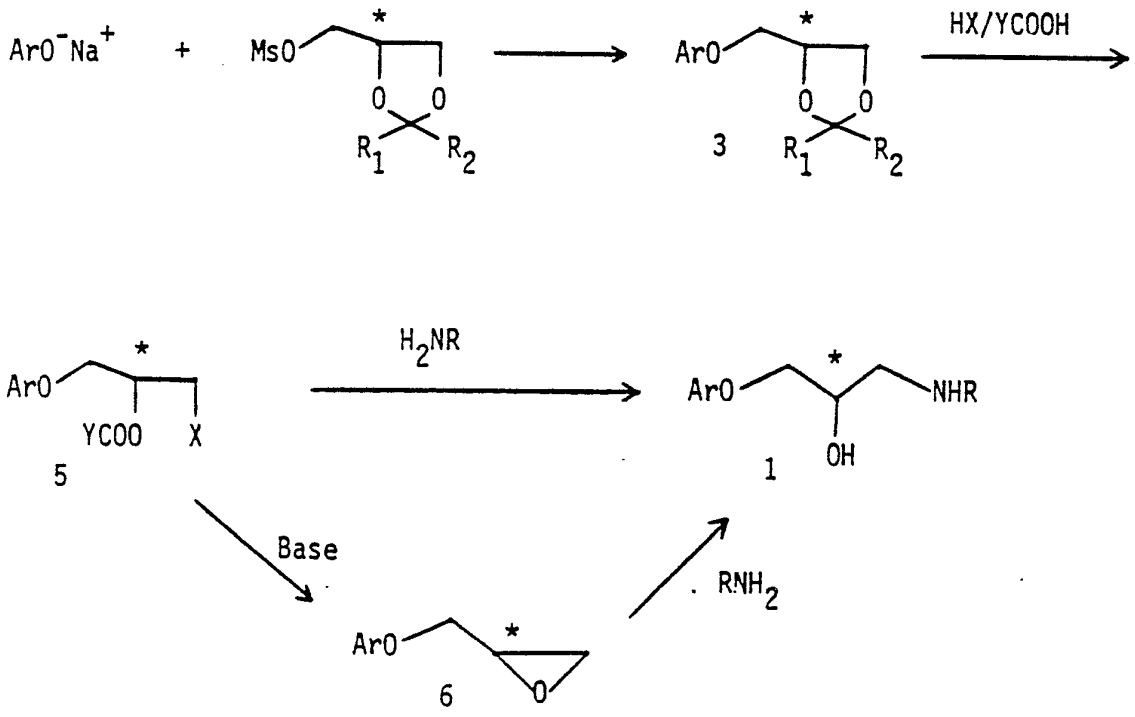


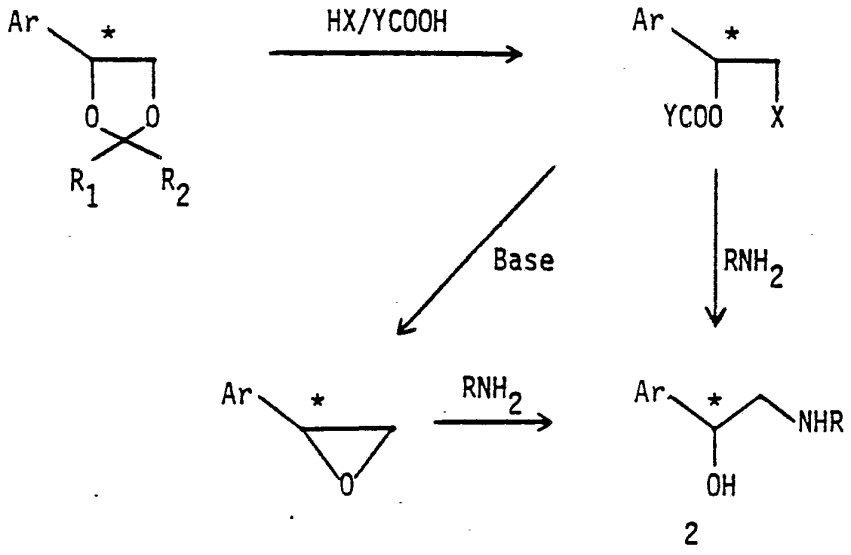
wherein R_3 is lower alkyl, aryl or aralkyl and A is a direct bond, alkylene of from 1 to about 10 carbon atoms or alkenylene of from 2 to about 10 carbon atoms.

The term "cycloalkyl" as used herein refers to cyclic saturated aliphatic radicals containing 3 to 6 carbon atoms in the ring, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

As an example, the method involves the utilization of an HBr/AcOH mixture to directly convert the aryloxypropanolamine. The method can be used in the synthesis of beta-agonists or beta-blockers.

The following reaction schemes summarize the process of the present invention.





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Referring to the scheme, the (R)-(-) or S-(+)-2,2-dimethyl-4-aryloxymethyl-1,3-dioxolane (3) can be made by known methods. For example, the S-enantiomer can be prepared readily by reacting an appropriate phenoxide with S-(+)-2,2-dimethyl-4-(hydroxymethyl)-1,3- dioxolane methanesulfonate or p-toluene-sulfonate.

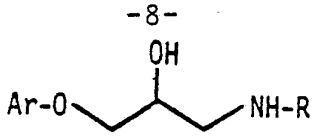
The aryloxypropanolamine (1) can be made by reacting the above dioxolane (or ketal) with HBr/Acetic acid, followed by amination with a selected amine.

If desired, the bromoacetoxy 5 is allowed to react with a suitable base to give the epoxide 6, which is then reacted with a selected amine to prepare the desired aryloxypropanolamine.

A suitable base for reaction with the bromoacetoxy would be a metal alkoxide, metal hydroxide, metal hydride, metal carbonate or metal bicarbonate wherein the metal is sodium, potassium or calcium, or an ammonium hydroxide or a suitable organic base. Preferred organic bases are pyridine, dimethylaminopyridine, dimethylaniline, quinoline, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4,3.0]non-5-ene (DBN) or tertiary alkylamines. Preferred bases are sodium or potassium methoxide, ethoxide or t-butoxide or a tertiary alkyl amine.

The arylethanolamines can be prepared as follows. The aryl ketal of 1,2-ethanediol can be converted to the corresponding bromoacetate by reacting it with HBr/AcOH. The resulting bromohydrin then can be cyclized to an epoxide by treating it with one equivalent of sodium methoxide. The arylethanolamine can be obtained by treating the epoxide with one equivalent of amine.

The following beta-adrenergic blocking agents, beta-agonists and partial agonists are representative of the compounds that can be made using the described process:



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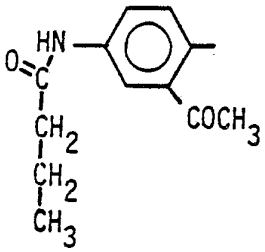
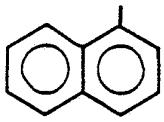
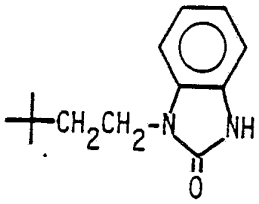
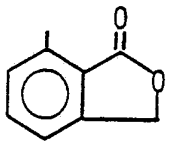
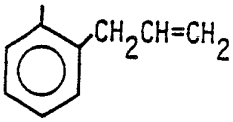
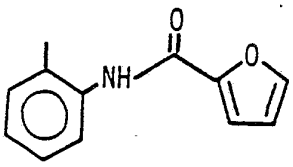
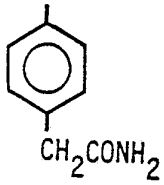
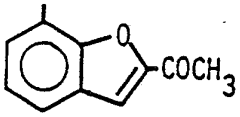
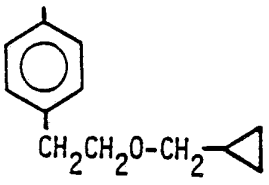
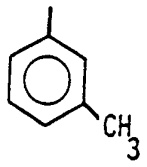
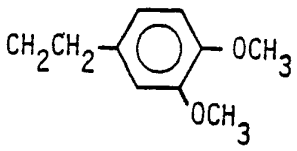
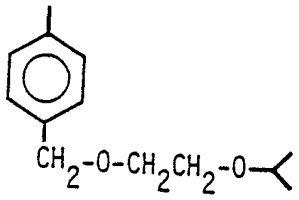
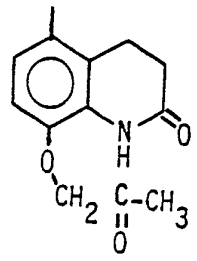
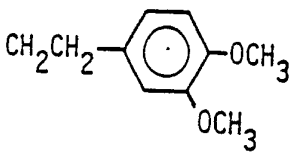
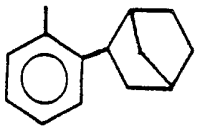
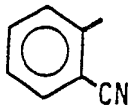
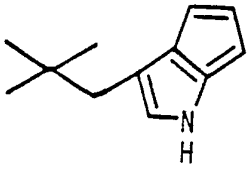
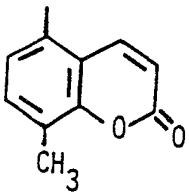
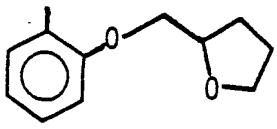
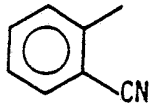
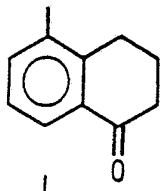
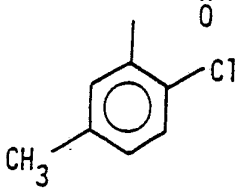
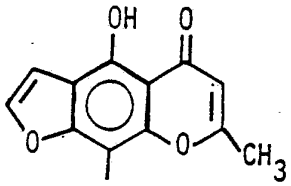
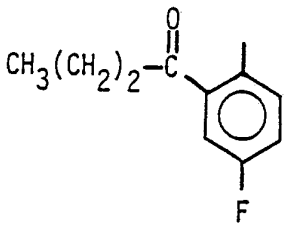
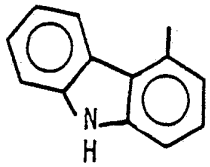
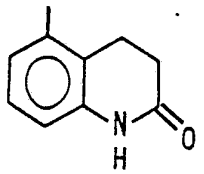
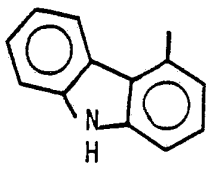
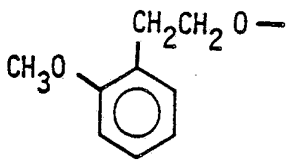
		Acebutolol
		Adimolol
		Afurolol
		Alprenolol
		Ancarolol
		Atenolol
		Befunolol
		Betaxolol

Ar	R	Compound
		Bevantolol
		Bisprolol
		Bometolol
		Bornaprolol
		Bucindolol
		Bucumolol
		Bufetolol

Ar	R	Compound
		Bunitrolol
		Bunalol
		Bupranolol
		Butocrolol
		Butofilolol
		Carazolol
		Carteolol
		Carvedilol

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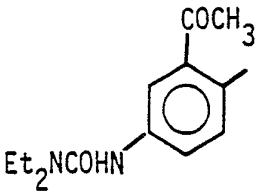
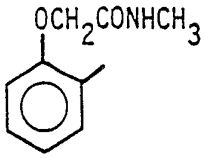
		Celiprolol
		Cetamolol
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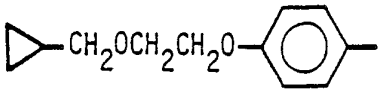
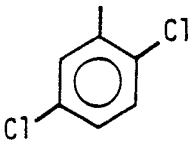
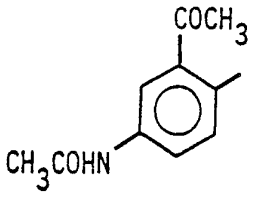
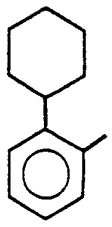
		Cidoprolol
		Cloranolol
		Diacetolol
		Exaprolol

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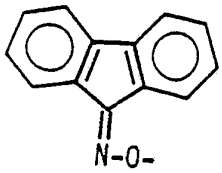
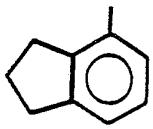
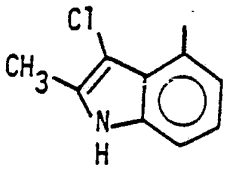
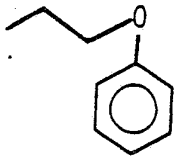
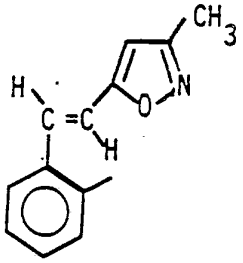
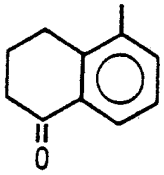
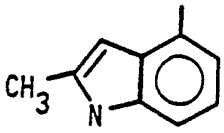
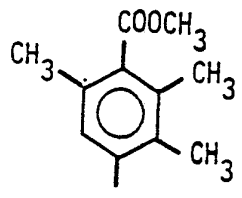
		IPS-339
		Indenolol
		Indopanolol
		Isoxaprolol
		Levobunolol
		Mepindolol
		Metipranolol

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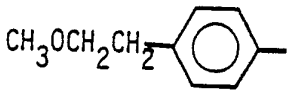
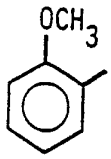
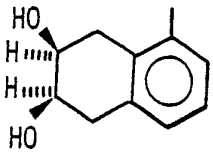
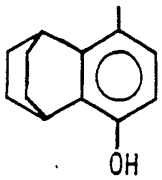
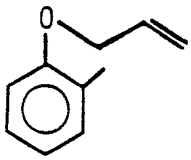
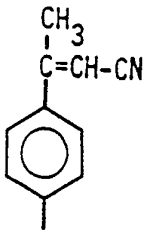
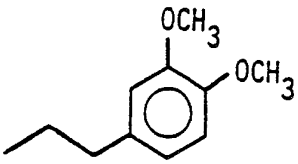
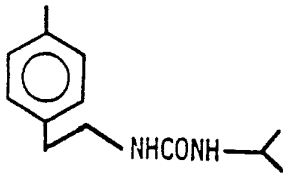
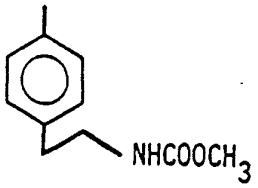
		Metoprolol
		Moprolol
		Nadolol
		Nafetolol
		Oxprenolol
		Pacrinolol
		Pafenolol
		Pamatolol

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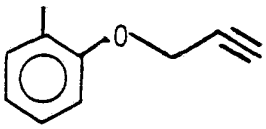
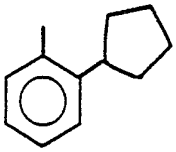
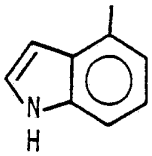
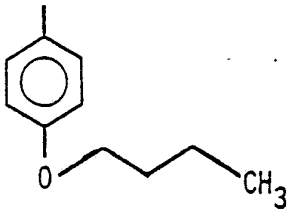
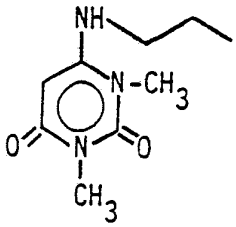
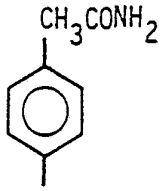
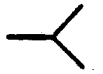
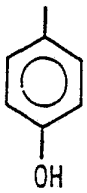
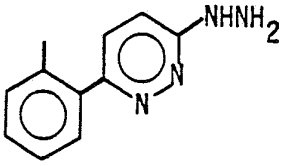
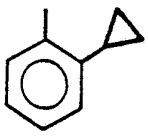
	+	Pargolol
	+	Penbutolol
		Pindolol
		Pirepolol
		Practolol
		Prenalterol
	+	Prizidilol
		Procinolol

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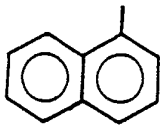
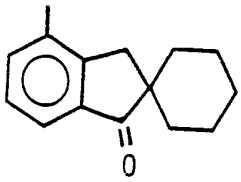
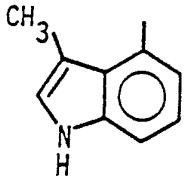
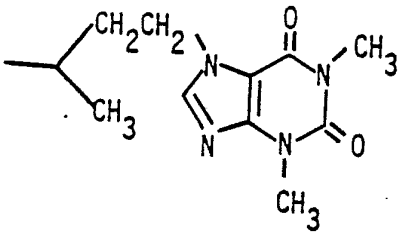
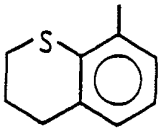
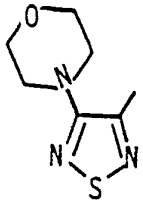
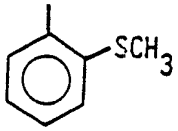
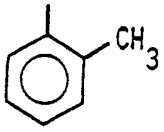
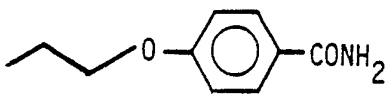
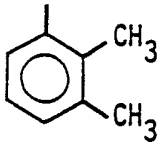
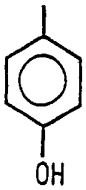
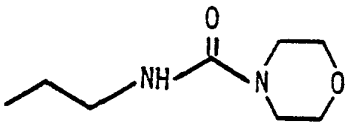
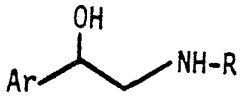
		Propranolol
		Spirendolol
		Teoprolol
		Tertatolol
		Timolol
		Tiprenolol
		Tolamolol
		Xibenolol
		Xamoterol



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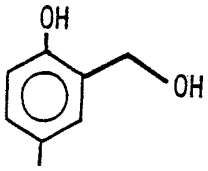
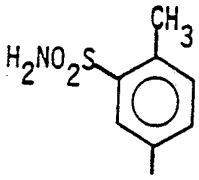
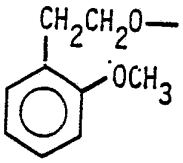
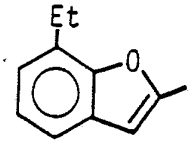
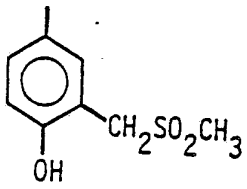
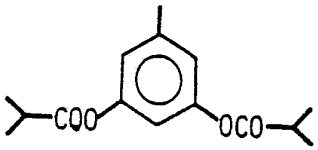
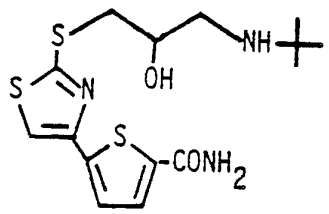
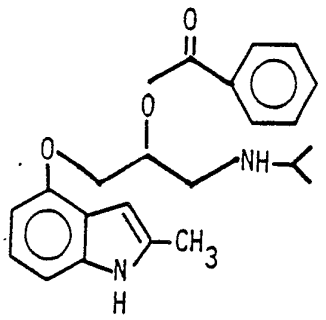
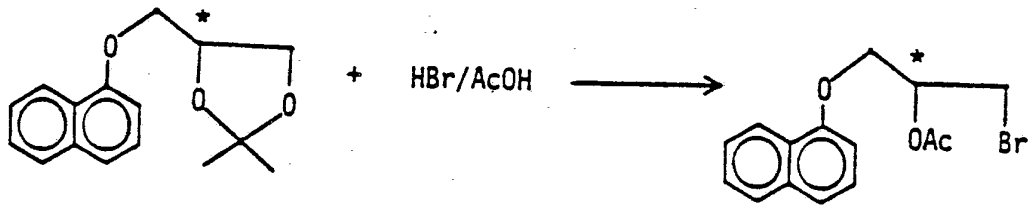
	+	Albuterol
		Amosulalol
	+	Bufuralol
	+	Sulfonterol
	+	Ibuterol

Miscellaneous Beta-Blockers	Compound
	Arotinolol
	Bopindolol

In order to illustrate the manner in which the above compounds may be made, reference is made to the following examples, which, however, are not meant to limit or restrict the scope of the invention in any respect.

EXAMPLE 1

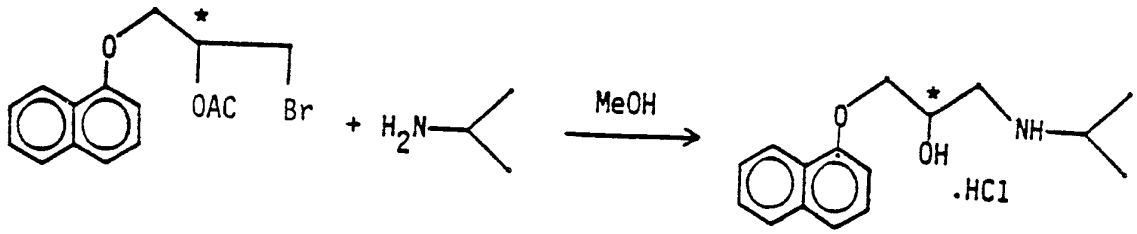
Preparation of (R)-(-)-2-(1-Naphthyloxy-3-bromo)propyl acetate



A mixture of (R)-(-)-2,2-dimethyl-4-napthyloxymethyl-1,3-dioxolane (100 g. 0.38 m), 30% HBr/AcOH (150 g) and AcOH (200 g) was allowed to stand at room temperature for 2 hours. Cyclohexane (1 L) was then added. The resulting mixture was stirred and cooled in an ice bath. The K_2CO_3 (300 g) was added portionwise. After the addition was completed, stirring was continued for 30 minutes. Ice water was then added slowly. The aqueous layer was discarded and the organic layer was further washed with a saturated solution of $NaHCO_3$. The extract was dried over $MgSO_4$ and evaporated to an oil (120 g, 96%). This was used in the next step without any further purification.

EXAMPLE 2

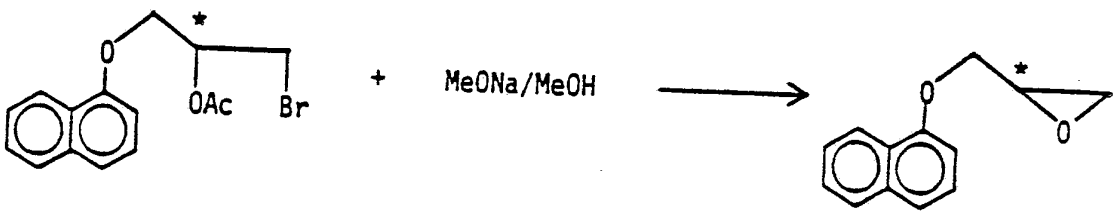
Preparation of (S)-(-)-propranolol - Method A



A solution of (R)-(-)-2-(1-napthyloxy-3-bromo)propyl acetate (20 g, 6.2 mM) and ispropylamine (5 g) in methanol (50 mL) was refluxed for 1 hour and evaporated to dryness. The residue was taken up with water, basified with K_2CO_3 and extracted twice with ether. The organic layers were combined, washed with water, dried over $MgSO_4$, filtered and acidified with hydrogen chloride. The solid precipitate was filtered and recrystallized from ethanol to afford 14.6 g (79.6%) of white crystalline product, m.p. 197-200° C, α_D^{25} = -26.1 (c 1, EtOH).

EXAMPLE 3

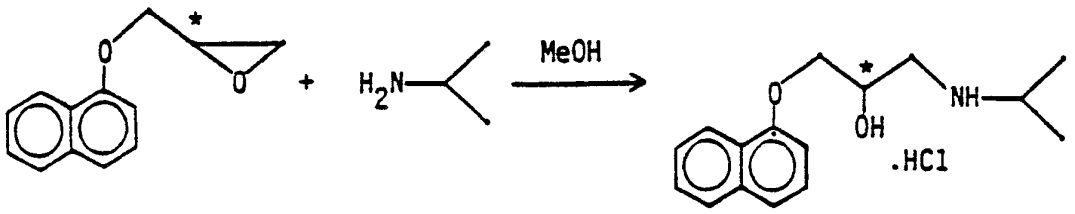
Preparation of (S)-(+)-glycidyl napthhthyl ether



To a solution of (R)-(-)-2-(1-napthyloxy-3-bromo)propyl acetate (120 g, 0.37 m) in methanol (50 mL) was added a solution of 25% MeONa in methanol (96 g). Sodium bromide was separated instantaneously. After stirring for 30 minutes, cyclohexane (1 L) was added to the mixture which was washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated to an oil (70 g, 95%). The crude material was distilled under reduced pressure to yield 62 g (85%) of pure product, bp 130-135° C (0.1-0.2 mmHg), $[\alpha]_D^{25}$ +27.1 (c 1.1, EtOH). NMR and IR were consistent with the assigned structure.

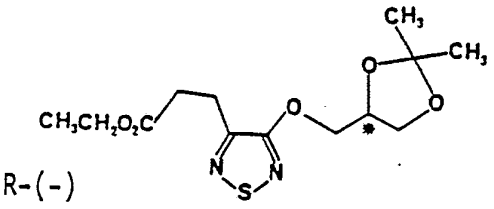
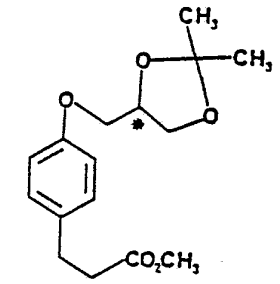
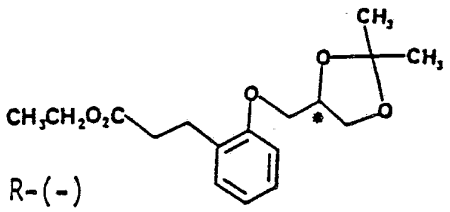
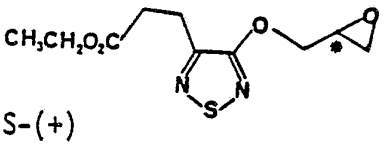
EXAMPLE 4

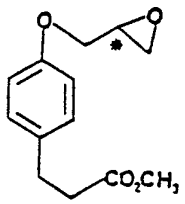
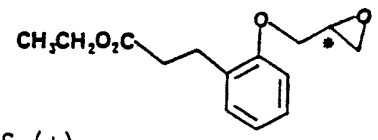
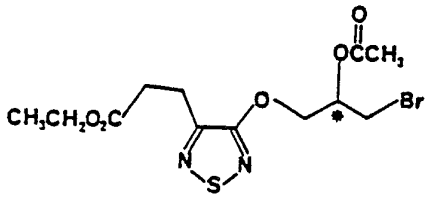
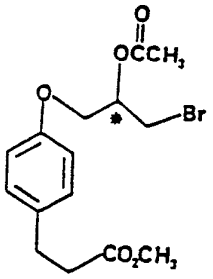
Preparation of (S)-(-)-propranolol - Method B

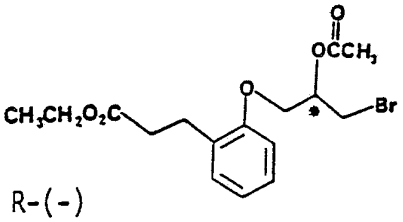
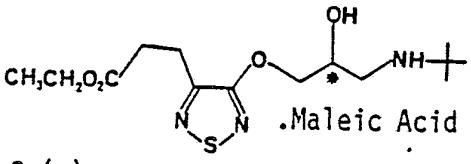
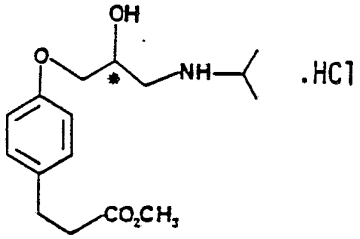
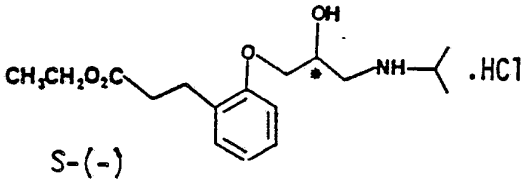


A solution of (S)-(+)-glycidyl naphthyl ether (20 g, 0.1 m) and isopropylamine (10 g, 0.17 m) in methanol (100 mL) was refluxed for 1 hour and evaporated to dryness. The residue was taken up with ether (200 mL), washed with water and dried over $MgSO_4$. After filtering, the filtrate was acidified with gaseous HCl. The crude solid was recrystallized from ethanol to afford 24 g (81%) of pure l.-propranolol, mp 198-200° C, $[\alpha]_D^{25}$ -26.8 (c 1, EtOH). NMR and IR were consistent with the assigned structure.

Using the same procedures as described in the above examples, the following compounds were prepared:

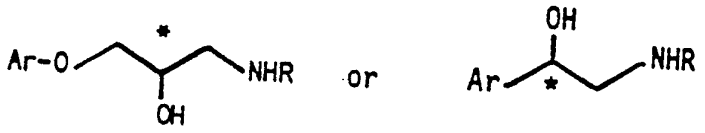
Compound	B.p., °C. (M.p.)	$[\alpha]_D^{25}$
 R-(-)	150-160 (0.1-0.2 mmHg)	-7.76 (neat)
 R-(-)	152-164 (0.1-0.3 mmHg)	-5.42 (neat)
 R-(-)	150-165 (1.2-1.8 mmHg)	-18.6 (c 1, EtOH)
 S-(+)	118-122 (0.2 mmHg)	+25.3 (c 1.5, EtOH)

Compound	B.p., °C. (M.p.)	$[\alpha]_D^{25}$
 S-(+)	150-156 (0.1-0.15 mmHg)	+7.9 (c 0.66, MeOH)
 S-(+)	140-155 (1.0-1.5 mmHg)	+13.08 (c 15, EtOH)
 R-(-)	Decomposed	-
 R-(-)	Decomposed	-

Compound	B.p., °C. (M.p.)	$[\alpha]_D^{25}$
 R-(-)	165-175 (1.00 mmHg)	-8.3 (c 14, EtOH)
 S-(-)	(115-118)	-10.5 (c 1, EtOH)
 S-(-)	(92-94)	-19.6 (c 1, MeOH
 S-(-)	(100-102)	-20.3 (c 1, EtOH)

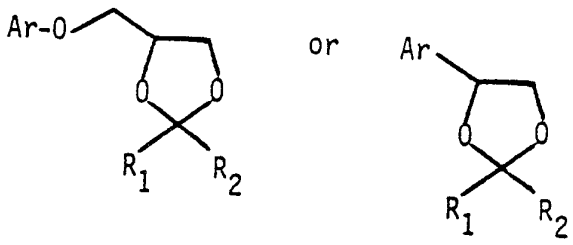
What is claimed is:

1. A method of preparing a racemic or chiral aryloxypropanolamine (1) or chiral arylethanolamine (2) of the formula

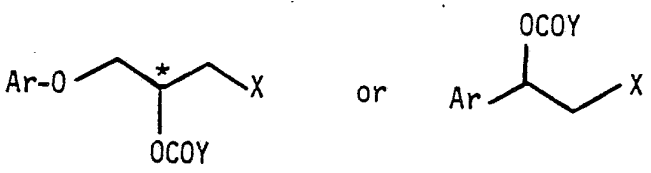


1 2

wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, aryl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $-NR_2COR_3$, $-NR_2CONR_3R_4$, $-NR_2SO_2R_3$, $-NR_2SO_2NR_3R_4$, or $-NR_2COOR_5$, where R_2, R_3, R_4, and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $-NR_2SO_2R_3$ or $-NR_2COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group, which method comprises: reacting a selected racemic or chiral dioxolane of the formula

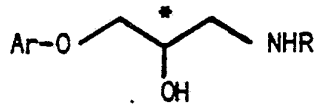


wherein Ar is defined as above and R_1 and R_2 are each independently hydrogen, loweralkyl, cycloloweralkyl, or R_1 and R_2 together with the carbon atom form a 3 to 6 member cycloalkyl group or aryl group, with a solution of HX, wherein X is chloro, bromo or iodo, in an organic acid of the formula Y-COOH wherein Y is hydrogen, loweralkyl or cycloalkyl to prepare a racemic or chiral compound of the formula



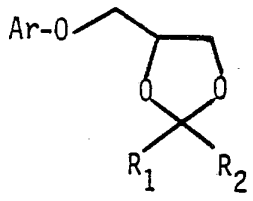
wherein X and Y are as defined above, and reacting said compound with a selected amine to prepare the desired aryloxypropanolamine or arylethanolamine.

2. A method of preparing a racemic or chiral aryloxypropanolamine of the formula

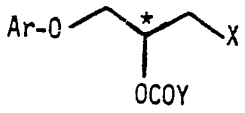


1

wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, aryl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $-NR_2COR_3$, $-NR_2CONR_3R_4$, $-NR_2SO_2R_3$, $-NR_2SO_2NR_3R_4$, or $-NR_2COOR_5$, where R_2, R_3, R_4, and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $-NR_2SO_2R_3$ or $-NR_2COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group, which method comprises: reacting a selected racemic or chiral dioxolane of the formula

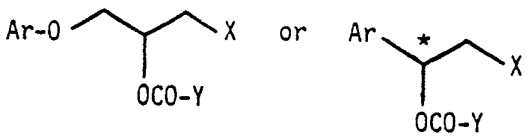


wherein Ar is defined as above and R_1 and R_2 are each independently hydrogen, loweralkyl, cycloloweralkyl, or R_1 and R_2 together with the carbon atom form a 3 to 6 member cycloalkyl group or aryl group, with a solution of HX, wherein X is chloro, bromo or iodo, in an organic acid of the formula Y-COOH wherein Y is hydrogen, loweralkyl or cycloalkyl to prepare a racemic or chiral compound of the formula

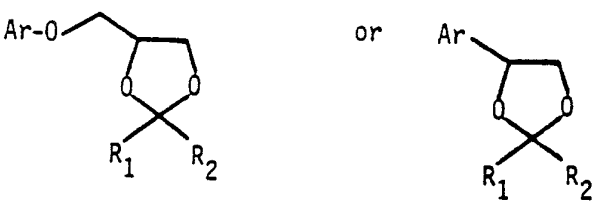


wherein X and Y are as defined above, and reacting said compound with a selected amine to prepare the desired aryloxypropanolamine or arylethanolamine.

3. A method of preparing a compound of the formula



wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl, X is chloro, bromo or iodo and Y is hydrogen, loweralkyl or cycloloweralkyl, which method comprises: reacting a selected racemic or chiral dioxolane of the formula



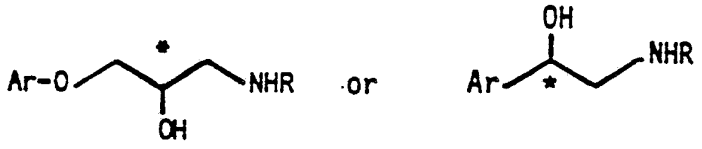
wherein Ar is defined as above and R_1 and R_2 are each independently hydrogen, loweralkyl, cycloloweralkyl, or R_1 and R_2 together with the carbon atom form a 3 to 6 member cycloalkyl group or aryl group, with a solution of HX, wherein X is defined as above, in an organic acid of the formula Y-COOH wherein Y is defined as above.

4. The method of Claim 3 wherein the mixture of strong acid of the formula HX in the organic acid of the formula Y-COOH comprises from 0.1 to 50% strong acid.

5. The method of Claim 3 wherein the strong acid is HBr and the organic acid is acetic acid.

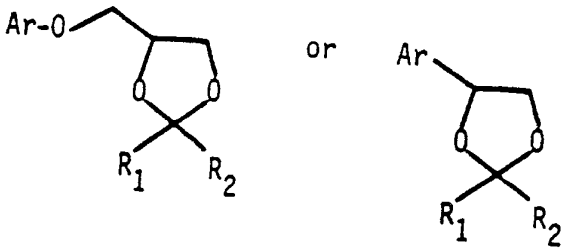
6. The method of Claim 5 wherein the HBr is present in the acetic acid in an amount of from 0.1 to 50% of the mixture.

7. A method of preparing a racemic or chiral aryloxypropanolamine (1) or chiral arylethanolamine (2) of the formula

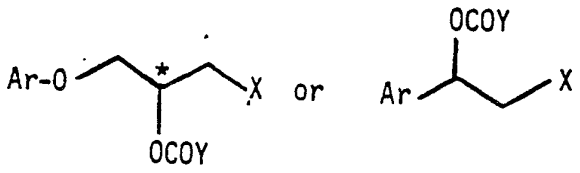


1 2

wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, aryl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $-NR_2COR_3$, $-NR_2CONR_3R_4$, $-NR_2SO_2R_3$, $-NR_2SO_2NR_3R_4$, or $-NR_2COOR_5$, where R_2, R_3, R_4, and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $-NR_2SO_2R_3$ or $-NR_2COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group, which method comprises: reacting a selected racemic or chiral dioxolane of the formula



wherein Ar is defined as above and R_1 and R_2 are each independently hydrogen, loweralkyl, cycloloweralkyl, or R_1 and R_2 together with the carbon atom form a 3 to 6 member cycloalkyl group or aryl group, with a solution of HX, wherein X is chloro, bromo or iodo, in an organic acid of the formula Y-COOH wherein Y is hydrogen, loweralkyl or cycloalkyl to prepare a racemic or chiral compound of the formula



wherein X and Y are as defined above, reacting said compound with a suitable base to prepare the appropriate epoxide, and reacting said epoxide with a selected amine to prepare the desired aryloxypropanolamine or arylethanolamine.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/02407

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): C07C 57/00, C07C 67/02, C07C 93/06, See Attachment
U.S. : 544/168, 544/224, 544/256, 544/312, See Attachment

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	544/168, 544/224, 544/256, 544/312, 546/158, 548/186, 548/186, 548/247, 548/303, 548/444, 548/516, 549/289, 549/310, 549/384, 549/467, 549/471, 549/491, See Attachment

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US,A, 4,202,978 (FAHRENHOLTZ ET AL) 13 May 1980 See col. 3-4, 7-8, 11-12, 13-14, 18-20, 23, 33-34, 39.	1-7
X	N, Agric. Biol. Chem., issued May 1982, Shinobu Iriuchijima et al., Asymmetric Hydrolysis of (±)-1,2-Diacetoxy-3-Chloro-propane and Its Related Compounds with Lipase. Synthesis of Optically pure(S)-Propranolol, Vol. 46, No. 5, pages 1153-1157. See pages 1153-54 and 1156.	1-7

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
05 February 1987	18 FEB 1987
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Hines Robert V. Hines 02/05/87

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ...., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

Group I: Claims 1-2, and 7, drawn to amines, classified in Class 564.

Group II: Claims 3-6, drawn to esters, classified in Class 560

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☒ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Attachment

I. CLASSIFICATION OF SUBJECT MATTER:

IPC(4): C07D 209/82, C07D 215/36, C07D 237/02, C07D 239/02, C07D 261/06, C07D 265/30, C07D 277/04, C07D 307/87, C07D 311/74, C07D 311/78, C07D 407/00, C07D 473/00; C07D 487/06

U.S. : 544/168, 544/224, 544/256, 544/312, 546/158, 548/186, 548/247, 548/303, 548/444, 548/516, 549/289, 549/310, 549/384, 549/467, 549/471, 549/491, 560/254, 564/304, 564/349

II. FIELDS SEARCHED:

U.S. : 560/254, 564/304, 564/349