

DESCRIPTIONProcess for Producing and Separating Diastereomeric
Urea Derivatives

The present application has been divided out of our Application No.83.24536 (2127020), referred to below as our "primary" Application, in which we have described and claimed a process permitting the resolution of optical isomers of certain beta-adrenergic aryl- or hetaryl-oxypropanolamines.

As explained in the specification of our primary Application, it is well established that many beta-adrenergic agents elicit more than a single biological effect following administration. Resolution of the optical isomers of these agents which contain asymmetric centers has, in many instances, demonstrated marked differences in potency between these isomers. In addition to increasing knowledge of receptor site topography, the pharmacologic profiles of the individual isomers may provide new and/or more desirable drug entities.

Previously, the optical isomers of β -adrenergic agents have most generally been obtained by one of three basic methods: 1) the fractional recrystallization of chiral acid salt derivatives; 2) synthesis of the single optical isomer using chiral epoxide

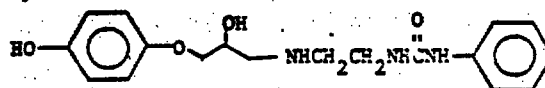
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intermediates; and, more recently, 3) column chromatography utilizing chiral stationary phases. The difficulties associated with application of these methods are well known to practitioners in the art: specifically, the tedious and time-consuming fractional recrystallizations and repeated chromatography, requisite chiral syntheses of epoxide intermediates with the attendant complications associated with stereospecific synthesis, and size limitation of quantities obtained via chromatography. Generally, preparation of a single enantiomer by these methods is quite expensive.

Another resolving method, derivatization with a chiral organic reagent, has been used for resolution of compounds which can form derivatives. β -Adrenergic agents in general have two functional moieties amenable to derivatization, i.e. secondary amino and alcohol functionalities. The resolution of amines and alcohols by derivatization with chiral acyl halides or isocyanates is well known in the chemical literature. The success of such a resolution strategy depends upon several factors, notably 1) formation of the diastereomeric derivatives in reasonably high yield, 2) facile separation of these diastereomers by chromatographic or crystallization techniques, and 3) the regeneration of the parent compound from the separated diastereomeric derivatives. To our knowledge, this technique has never been utilized for the resolution of β -adrenergic propanolamines.

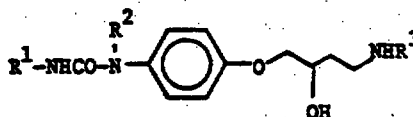
The following references disclose β -adrenergic propanolamines having a urea moiety incorporated into their structure.

1. O'Donnell, et al, Clin. Exp. Pharmacol., 8/6, 614-615 (1981) disclose a β -adrenergic agent (ICI 89963) with a urea moiety in the terminal alkyl portion of the structure.



ICI 89963

2. Eckardt, et al., Die Pharmazie, 30, 633-637 (1975) disclose β -blocking propanolamines with urea substituents on the aryl portion of the molecule:



Eckardt, et al.

These urea compounds differ structurally from the urea intermediates of the instant process as the propanolamine nitrogen of the reference compounds is not a component of the urea grouping.

The next grouping of references relate to methods of resolution of optical isomers which are deemed most relevant to the instant process described herein.

3. J. Jacques, A. Collet, S. H. Wilen, in "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, New York, N.Y. (1981), pp. 330-335. This reference describes, among other things, formation and separation of diastereomers comprising covalent derivatives of amines and alcohols. Specifically, amines may be resolved through conversion into diastereomeric ureas by reaction with optically active isocyanates; and, following separation of the diastereomeric ureas by crystallization or by chromatography, the resolved amine is recovered through pyrolysis.

4. F. C. Whitmore in "Organic Chemistry", D. Van Nostrand Co., New York, N.Y. (1937), p. 551. This reference reports that dl-3-amino-lactic aldehyde dimethyl acetal, $H_2NCH_2CHOHCH(OCH_3)_2$, gave diastereomeric ureas when treated with l-menthyl isocyanate, as part
5 of a scheme to prepare optically active glyceraldehydes.

5. Kolomiets, et al., Zh. Org. Khim., English Edition, 16/5, pp. 854-857 (1980). This reference describes kinetic resolution of secondary alcohols and amines using S-(-)- α -phenylethylisocyanate.

It is appreciated by the practitioner in the art, that
10 derivatization of β -adrenergic aryloxypropanolamines might be expected to present difficulties by virtue of the molecule containing two reactive functionalities, e.g. both an amine and an alcohol moiety.

Reference 4., supra, is the only example of which we are aware that reports diastereomeric urea derivatization by isocyanate
15 treatment of a molecule containing both amino and hydroxy moieties. The compound being derivatized in the work mentioned by Whitmore is not related to the β -adrenergic propanolamine structure. The terminal primary amino group as opposed to the secondary hydroxyl in
 $H_2NCH_2CHOH(OCH_3)_2$ would be expected to be more accessible sterically
20 to electrophilic attack by an isocyanate. Any steric advantage of the amino group is negated in β -adrenergic structures in which the amino nitrogen is further substituted with an alkyl group, which is usually branched, thereby giving a more hindered secondary amine. It would
reasonably be expected prior to the instant invention that reaction
25 of an optically active isocyanate and a β -adrenergic aryloxypropanolamine would result in a complex product mixture containing both diastereomeric ureas and carbamates. In practice, it is discovered that the reaction

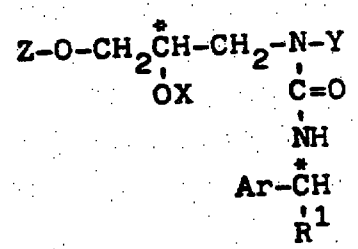
takes place preferentially at the site of the amine moiety, even when sterically hindered, giving predominantly as novel intermediates the diastereomeric derivatives. This reaction selectivity forms the basis for the first step of the process of the present invention, as also for the first step of the process of our primary Application.

The process of our primary Application comprises treatment of the racemic mixture of β -adrenergic propanolamines with a chiral isocyanate to give diastereomeric urea intermediates, separation of these into the individual diastereomers, and facile generation of each optical isomer of the starting amine by cleavage of the intermediate urea compound with hydrazine hydrate.

In the present Application, however, we are concerned only with the first two of the three steps just mentioned.

According to the present invention, in fact, we provide a process for producing and separating intermediate urea derivatives of Formula III

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(III)

wherein

Z is substituted or unsubstituted aryl group for example phenyl, tetralyl, indanyl, indenyl or naphthyl; or a substituted or unsubstituted hetaryl group for example pyridine, benzopyridine, pyrrole, benzo-pyrrole, furan, benzofuran, thiophene, benzothiophene, pyrimidine, or thiadizole, with the substituent or substituents bonded to Z being a member or members selected from the group of lower alkyl, lower alkoxy, lower alkenyl, lower alkenyloxy, lower alkynyl, lower alkynyloxy, lower alkylthio, lower alkanoyl, hydroxy-lower alkyl, cyano, lower cycloalkyl, lower cycloalkenyl, carbamoyl, lower alkylcarbamoyl, carbamoyl-lower alkyl, lower alkyl carbamoyl-lower alkoxy, lower alkyl-lower alkoxy,

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lower

alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower

alkenylthio, lower alkylthio-lower alkyl, lower alkoxy-lower alkylthio,

halogen, halogen-lower alkyl, hydroxyl, carboxyl,

N,N-di-lower alkyl carbamoyl,

N-lower alkyl carbamoyl-lower alkyl, N,N-di-lower alkyl carbamoyl-lower

alkyl, lower alkanoylamino-lower alkenyl, N-lower alkylamino, N,N-

di-lower alkylamino, lower alkoxy-carbonyl, lower alkoxy-carbonylamino,

lower alkoxy-carbonylamino-lower alkyl, lower alkoxy-carbonylamino-lower

alkenyl, lower alkoxy-carbonylamino-lower alkoxy, lower alkyl-carbonyl-

amino-lower alkyl, N'-lower alkyl-ureido, N,N'-di-lower alkyl-ureido,

lower alkylsulfonylamino,

nitro,

lower alkenoyl,

and N-morpholino;

the word "lower" having the signification "up to C_6 ";Y is C_1 to C_{10} alkyl or AB

wherein

A is an alkyl chain from 1 to 10 carbons, branched or unbranched, and

B is a substituted or unsubstituted aryl or hetaryl group;

X is hydrogen or R-CO-

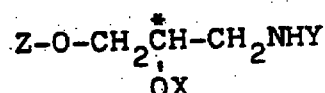
wherein

R is C₁-C₁₀ alkyl, phenyl, substituted phenyl, or alkylphenyl;

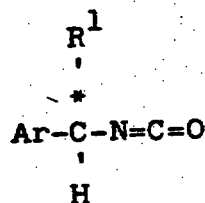
Ar represents an aryl group, for example phenyl, substituted phenyl or naphthyl; and

R¹ is C₁-C₆ alkyl;

said process comprising reacting a compound of Formula I



wherein Z, Y and X are as previously defined with a compound of Formula II



wherein Ar and R¹ are as previously defined so as to produce a pair of diastereomeric urea derivatives of Formula III and then separating said pair of diastereomeric urea derivatives of Formula III; said separating step being achieved by the use in the said reacting step of a reaction liquid in which one of said pair of diastereomeric urea derivatives of Formula III is soluble and the other of said pair of derivatives is insoluble.

The present improved process is convenient, and amenable to large-scale manufacture.

The following are optional or preferred features of the process of the present invention:-

- (a) Z is an ortho substituted phenyl ring;
- (b) Z is an ortho substituted pyridine ring;
- (c) A is a C₂-C₄ alkyl chain, branched or unbranched, and B is an indole ring system;
- (d) X is hydrogen;
- (e) R¹ is methyl and Ar is 1-naphthyl.

It is preferred that X have ortho-substitution.

Where B is aryl, it may for example be phenyl, and, where B is hetaryl, it may additionally be a radical derived from, for example,

pyridine, benzopyridine, pyrrole, benzopyrrole, furan, benzofuran, thiophene, benzothiophene, pyrrolidine, or piperidine. Substituent groups attached to A comprise lower alkyl, alkoxy, alkenyl, nitro, hydroxy, amino, cyano, or halogen.

The substituent groups of the radicals Z and Y, listed above, may be more specifically defined. The term lower alkyl as used hereinabove denotes cyclic, straight and branched chain alkyl groups of 1-6 carbon atoms inclusive, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, pentyl, or cyclohexyl radicals bonded in any desired position.

The term lower alkenyl denotes straight and branched chain alkenyl groups of 2-6 carbon atoms, especially allyl or methallyl radicals.

The term lower alkynyl includes the straight or branched chain alkynyl groups of 2-6 carbons, with the propargyl radical being especially suited.

The term lower alkyloxy or lower alkoxy denotes straight or branched chain alkoxy groups of 1-6 carbon atoms, for example, methoxy, ethoxy, propoxy, butoxy, and the like.

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The term lower alkenyloxy denotes straight and branched chain lower alkenyloxy groups and the positional isomers thereof, having 2-6 carbons, for example, ethenoxy, propenoxy, butenoxy, and the like.

The term lower alkynyloxy embraces straight and branched chain alkynyloxy groups of 2-6 carbon atoms, such as ethynyloxy, 2-propynyloxy, 3-butynyloxy, and the like.

The term lower alkoxy-lower alkyl embraces methoxymethyl, ethoxymethyl, isopropoxyethyl, and the like. The term lower alkoxy-lower alkoxy embraces for example methoxymethoxy, methoxyethoxy, ethoxyethoxy, ethoxyisopropoxy, and the like. The term hydroxy-lower alkyl is, for example, hydroxymethyl, 1- or 2- hydroxyethyl and the like.

The term lower alkylthio is, for example, methylthio, ethylthio, isopropylthio, n-butylthio, and the like. The term lower alkenylthio is illustrated by 1-propenylthio, 1-butenylthio, 3-pentenylthio, and the like. Lower alkylthio-lower alkyl is illustrated by methylthiomethyl, methylthioethyl, 2-ethylthioethyl, and the like. Lower alkoxy-lower alkylthio is illustrated by methoxymethylthio, ethoxymethylthio, and the like.

The term halogen is depicted by fluorine, chlorine, bromine, and iodine, especially fluorine or chlorine. The term halogen-lower alkyl is exemplified by trifluoromethyl, trichloromethyl, and the like.

It should also be understood that certain substituents as in the group set forth hereinabove may be attached to the 2 ring at two sites, usually adjoining ring atoms, to give, for example: tetralins, tetralones, indanes, indanones, indenenes, and the like.

Adrenergic propanolamines embraced by structure I for the purpose of this invention are exemplified by the following beneficial

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drugs which contain centers of asymmetry. Exemplary drugs are
 acebutolol or N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-
 phenyl]butanamide; alprenolol or 1-[(1-methylethyl)amino]-3-[2-(2-
 propenyl)-phenoxy]-2-propanol; atenolol or 1-p-carbamoylmethyl-
 5 phenoxy-3-isopropylamino-2-propanol; bevantolol or 1-[(3,4-dimethoxy-
 phenethyl)amino]-3-(m-tolyloxy)-2-propanol; buprenolol or 1-(tert.-
 butylamino)-3-[(6-chloro-m-tolyl)oxy]-2-propanol; bunitrolol or 2-
 [3-[1,1-dimethylethyl)amino]-2-hydroxypropoxy]benzonitrile; bunolol
 or 5-[3-(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-1(2H)-
 10 naphthalenone; exaprolol or 1-(o-cyclohexylphenoxy)-3-(isopropylamino)-
 2-propanol; indanolol or 1-[indan-4-yloxy]-3-[1-methylethylamino]-
 2-propanol; metoprolol or 1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-
 2-propanol; moprolol or 1-(2-methoxyphenoxy)-3-[(1-methylethyl)amino]-
 2-propanol; oxprenolol or 1-(isopropylamino)-2-hydroxy-3-[o-(allyloxy)-
 15 phenoxy]propane; pamatolol or methyl-[p-[2-hydroxy-3-(isopropylamino)-
 propoxy]phenethyl]carbamate; penbutolol or 1-(2-cyclopentylphenoxy)-
 3-[(1,1-dimethylethyl)amino]-2-propanol; pargolol or 1-(tert.-butylamino)-
 3-[o-(2-propynyloxy)phenoxy]-2-propanol; procinolol or 1-(o-cyclo-
 propylphenoxy)-3-(isopropylamino)-2-propanol; practolol or 1-(4-
 20 acetamidophenoxy)-3-isopropylamino-2-propanol; tiprenolol or 1-[(1-
 methylethyl)amino]-3-[2-(methylthio)-phenoxy]-2-propanol; tolamolol
 or 4-[2-[[2-hydroxy-3-(2-methylphenoxy)propyl]amino]ethoxy]benzamide;
 toliprolol or 1-(isopropylamino)-3-(m-tolyloxy)-2-propanol; nadolol
 or 1-(tert.-butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-
 25 naphthyl)oxy]-2-propanol; pindolol or 1-(indol-4-yloxy)-3-(isopropyl-
 amino)-2-propanol; and timolol or 1-(tert.-butylamino)-3-[(4-morpholino-
 1,2,5-thiadiazol-3-yl)oxy]-2-propanol. These beta-adrenergic propanol-
 amines are known to the art, appearing in the Merck Index, Unlisted

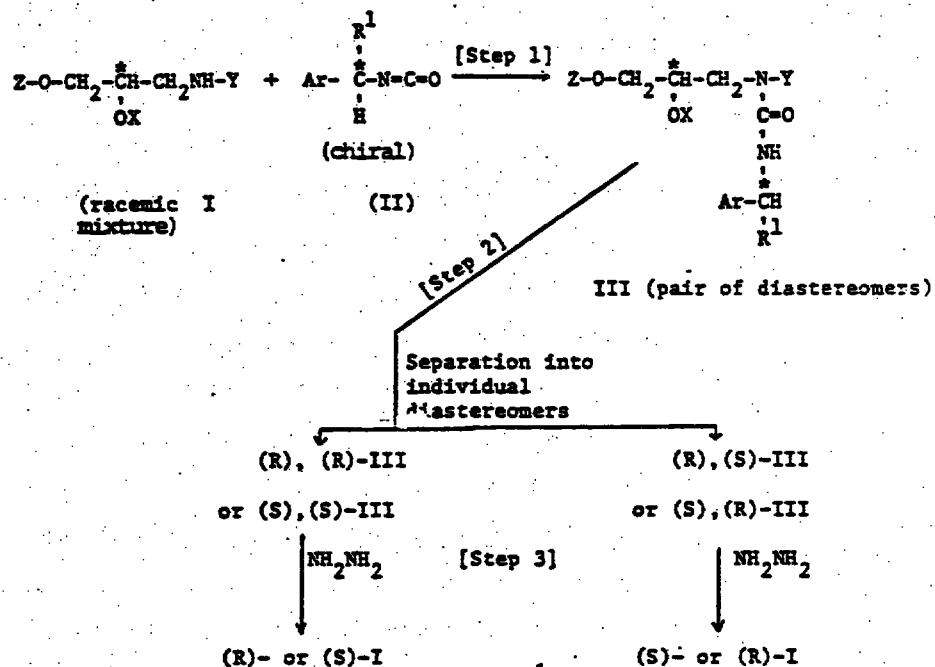
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Drugs, USAN and USP Dictionary of Drug Names, and Annual Reports in Medicinal Chemistry, Vol. 10, pages 51-60 (1975), and ibid., Vol. 14, pages 81-90 (1979).

Certain conventions are used by those skilled in the art to
5 designate optical rotation and spatial configuration of optical isomers. Individual enantiomers are commonly designated according to the optical rotation they effect, by (+) and (-), (l) and (d), or combinations of these symbols. The symbols (L) and (D) and the symbols (S) and (R), which stand for sinister and rectus, respectively, designate an absolute
10 spatial configuration of the enantiomer. A complete resolution utilizing the instant process is detailed in the following section entitled Description of Specific Embodiments. Assignment of absolute configuration to the enantiomers separated therein is tentative and is based on the usual assignment of S-configuration to the β -adrenergic aryloxypropanol-
15 amine enantiomer with negative rotation.

The following flow chart, Scheme 1, illustrates the resolution of a racemic mixture of β -adrenergic propanolamines utilizing the processes of our primary Application (the entire Scheme) and of the present Application (all but the final cleavages with hydrazine hydrate).

Scheme 1



In Scheme 1, X, Y, and Z are as defined above; Ar represents an aryl group such as phenyl, substituted phenyl or naphthyl, preferably 1-naphthyl; R¹ is a C₁-C₆ alkyl group, preferably methyl; and an asterisk denotes centers of asymmetry in the molecule. It is to be understood that other optically active isocyanates, e.g. menthyl isocyanate, may also be used in the instant process.

Step 1 of the Scheme outlined above involves the reaction of the adrenergic propanolamine with a chiral isocyanate of structure II to give a pair of novel diastereomeric ureas of Formula III. The reaction of step 1 is accomplished simply by stirring together equimolar quantities of the adrenergic amine, in its free base form,

and the chiral isocyanate in an inert organic liquid medium for several hours at approximately 25° C. The temperature can range from ambient room temperature up to the reflux temperature of the particular organic liquid used as reaction medium. This reaction is usually complete within four to eight hours. Suitable reaction liquids include but are not limited to benzene, tetrahydrofuran, dibutyl-ether, dimethoxyethane, etc. A preferred reaction liquid is benzene.

In the process of the present invention, as already indicated, an appropriate reaction liquid is chosen which permits the separation of the diastereomeric ureas by virtue of one of the diastereomers being soluble in the liquid and the other being insoluble.

The subject process, as mentioned, is particularly adaptable to large-scale operation, and in that respect is both economical and convenient. The process may for example comprise:

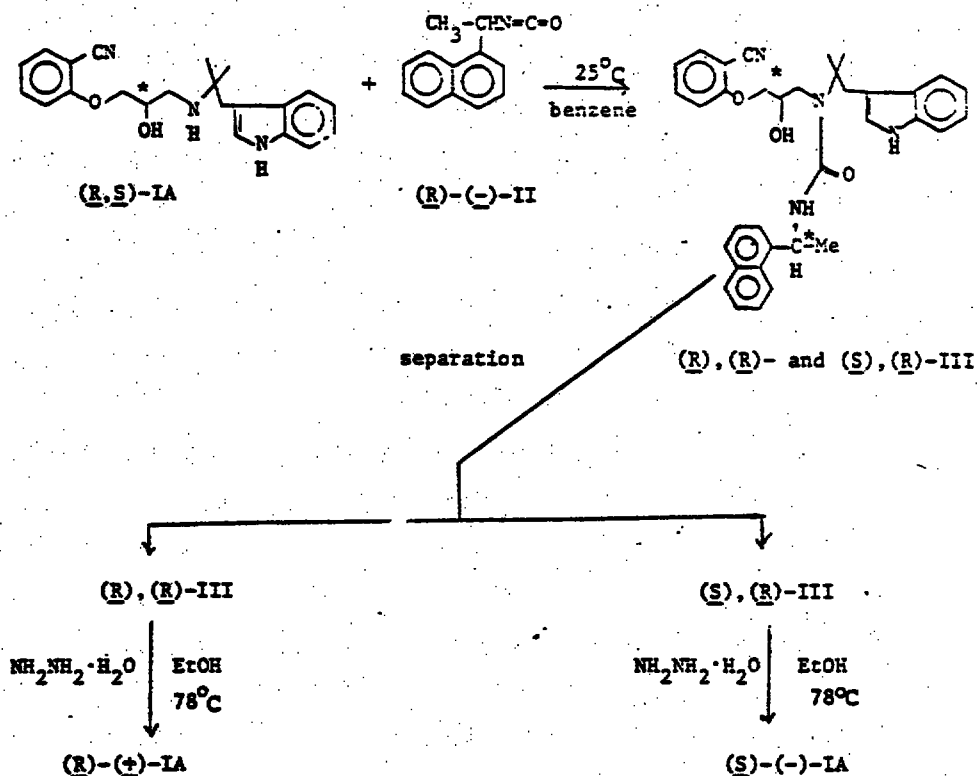
- (1) treating an appropriate β -adrenergic aryl- or hetaryl-oxypropanolamine, in the form of a racemic mixture, with a chiral isocyanate such as resolved 1-(1-naphthyl) ethyl isocyanate, by stirring for six to 12 hours in an inert organic liquid medium such as benzene at a temperature of from about ambient room temperature up to the reflux temperature of the organic liquid, thereby giving a pair of diastereomeric ureas (III);
- (2) separation of the diastereomeric pair into individual diastereomers by virtue of one of them being soluble, and the other insoluble, in the benzene or other inert organic liquid medium employed.

The process of this invention is further illustrated by the following examples, but these examples should not be construed as limiting the scope of the present invention. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. All temperatures are expressed in degrees Celsius. Optical rotation measurements were obtained on a Bendix-NPL 1169 automatic polarimeter with digital readout. The (R)-(-)-(1-naphthyl) ethyl isocyanate can be prepared as reported in the literature (Pirkle, et al, J. Org. Chem., 39 (1974) pages 3904-3906) or is available commercially (Aldrich Chemical Company).

Scheme 2 illustrates a specific procedure carried out with bucindolol (IA), which is an antihypertensive agent currently under clinical investigation. Like Scheme 1,

Scheme 2 illustrates the utilization of both our primary Application (the entire Scheme) and the present Application (all but the final cleavages with hydrazine hydrate).

Scheme 2



In examples which follow, the nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the ^2H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), or doublet (d). Abbreviations employed are DMSO- d_6 (deuterodimethylsulfoxide), CDCl_3 (deuteriochloroform) and are otherwise

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conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

EXAMPLE 1

Diastereomeric Urea Derivatives of Bucindolol

A hot solution of bucindolol hydrochloride salt (100 g, 0.28 mole) and 2.5 L of H_2O was made basic with a 10% solution of NaOH. Bucindolol is 2-[2-hydroxy-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]propoxy]benzonitrile; cf: Kreighbaum, et al, U.S. Patent No. 4,234,595 patented November 18, 1980, and Journal of Medicinal Chemistry, 23:3, 285-289 (1980). After being allowed to cool, the aqueous layer of the basic mixture was decanted and the residual gum rinsed with H_2O and crystallized from isopropyl alcohol (500 ml) to provide 81 g of bucindolol free base, m.p. $126-128^\circ\text{C}$. The aqueous layer was allowed to stand overnight at 15°C , and a precipitate was collected by filtration, washed with H_2O , and dried in air overnight to give a further 3.5 g of bucindolol free base. This material, a mixture of (R,S)-bucindolol base, was then derivatized.

A mixture of (R,S)-bucindolol base (1.8 g, 0.005 mole), (R)-(-)-1-(1-naphthyl)-ethylisocyanate (1.0 g, 0.005 mole), and benzene (100 mL) was stirred at 25°C for 6 hrs. A white solid was removed by filtration and dried in air to give 1.24 g of (S), (R)-N-[3-(2-cyanophenoxy)-2-hydroxypropyl]-N-[1,1-dimethyl-2-(1H-indol-3-yl)-ethyl]-N'-[1-(1-naphthyl)ethyl]urea. This urea derivative melted at $167-168^\circ\text{C}$ and gave a single spot on TLC (silica gel; CH_2Cl_2 -L. ethylacetate 9:1) and rotation of $[\alpha]_D^{25} -14^\circ$ (C 0.5%, CH_3OH).

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Anal. Calcd. for $C_{35}H_{36}N_4O_3$: C, 74.98; H, 6.48; N, 10.00.

Found: C, 74.89; H, 6.46; N, 9.74.

NMR (DMSO- d_6): 1.38 (6,s); 1.52 (3,d [6.7 Hz]); 3.35 (4,m);
3.94 (3,m); 5.70 (1,m); 6.23 (1,bs); 7.01 (5,m); 7.59 (11,m); 8.27 (1,d
5 [9.5 Hz]); 10.72 (1,bs).

IR (KBr): 745, 1110, 1260, 1490, 1530, 1600, 1630, 2230,
2930, 2970, 3050, 3350, and 3410 cm^{-1} .

The benzene filtrate from above was concentrated to dryness
and the residual material chromatographed on silica gel eluting with
10 CH_2Cl_2 -Ethylacetate (9:1) to give 0.70 g of (R), (R)-N-[3-(2-cyanophenoxy)-
2-hydroxypropyl]-N-[1,1-dimethyl-2-(1H-indol-3-yl)ethyl]-N'-[1-(1-
naphthyl)ethyl]urea as a foam. This material which did not crystallize
had a rotation of $[\alpha]_D^{25} -119^\circ$ (C 0.5%, CH_3OH).

Anal. Calcd. for $C_{35}H_{36}N_4O_3 \cdot \frac{1}{2}EtOAc$: C, 73.49; H, 6.67;
15 N, 9.27. Found: C, 73.29; H, 6.60; N, 9.18.

NMR (DMSO- d_6): 1.36 (3,s); 1.52 (6,m); 3.36 (4,m); 3.92 (3,m);
5.76 (1,m); 6.30 (1,bs); 7.00 (5,m); 7.55 (11,m); 8.26 (1,d [9.0 Hz]);
10.78 (1,bs).

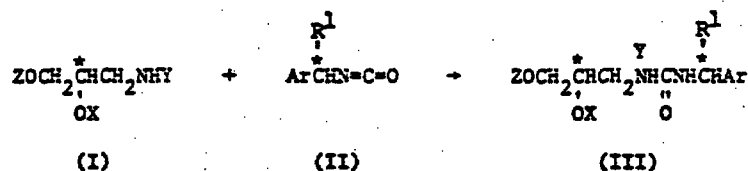
IR (KBr): 745, 1115, 1260, 1495, 1540, 1600, 1635, 2220, 2930,
20 2980, 3060, 3350, and 3420 cm^{-1} .

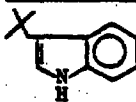
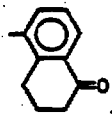
Treating racemic mixtures of other Formula I adrenergic
amines with chiral isocyanates (II) using reaction procedures similar
to those outlined above gives diastereomeric urea intermediates. Some
additional examples of these are listed in Table 1.

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Table 1

Adrenergic Propanolamine Urea Derivatives



5	Example	I			II	
		X	Y	Z	R	Ar
	2	H		2-cyanopyridyl	Me	phenyl
	3	H	1-Pr	2-(2-propenyl)phenyl	Me	1-naphthyl
	4	H	1-Pr	1-naphthyl	Me	1-naphthyl
	5	H	t-Bu		Me	phenyl
10	6	H	1-Pr	2-(2-propenyloxy)-phenyl	Me	phenyl
	7	H	1-Pr	4-(1H-indolyl)	Et	phenyl
	8	H	1-Pr	4-acetanilide	Me	1-naphthyl
	9	H	1-Pr	2-(methylthio)phenyl	Me	1-naphthyl
15	10	H	1-Pr	2-cyanopyridyl	Et	1-naphthyl
	11	H	t-Bu	2-cyanopyridyl	Me	4-nitrophenyl
	12	acetyl	2-(benzothiophen-3-yl)-1,1-dimethylethyl	2-cyanopyridyl	Me	1-naphthyl
20	13	H	2-(1H-indol-3-yl)-1,1-dimethylethyl	2-cyanopyridyl	Me	1-naphthyl

Please note that in Table 1 and throughout this document

1-Pr means isopropyl,

t-Bu means tertiary butyl,

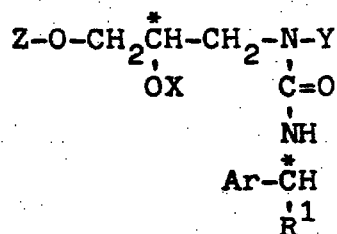
Me means methyl, and

Et means ethyl. Also degrees are given in degrees Centigrade.

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CLAIMS

1. A process for producing and separating intermediate urea derivatives of Formula III



(III)

wherein

- Z is substituted or unsubstituted aryl group for example phenyl, tetralyl, indanyl, indenyl or naphthyl; or a substituted or unsubstituted hetaryl group for example pyridine, benzopyridine, pyrrole, benzopyrrole, furan, benzofuran, thiophene, benzothiophene, pyrimidine, or thiadizole, with the substituent or substituents bonded to Z being a member or members selected from the group of lower alkyl, lower alkoxy, lower alkenyl, lower alkenyloxy, lower alkynyl, lower alkynyloxy, lower alkylthio, lower alkanoyl, hydroxy-lower alkyl, cyano, lower cycloalkyl, lower cycloalkenyl, carbamoyl, lower alkylcarbamoyl, carbamoyl-lower alkyl, lower alkyl carbamoyl-lower alkoxy, lower alkyl-lower alkoxy,



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lower

alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower

alkenylthio, lower alkylthio-lower alkyl, lower alkoxy-lower alkylthio,

halogen, halogen-lower alkyl, hydroxyl, carboxyl,

N,N-dilower alkyl carbamoyl,

N-lower alkyl carbamoyl-lower alkyl, N,N-di-lower alkyl carbamoyl-lower

alkyl, lower alkanylamino-lower alkenyl, N-lower alkylamino, N,N-

di-lower alkylamino, lower alkoxycarbonyl, lower alkoxy-carbonylamino,

lower alkoxy-carbonylamino-lower alkyl, lower alkoxycarbonylamino-lower

alkenyl, lower alkoxycarbonylamino-lower alkoxy, lower alkylcarbonyl-

amino-lower alkyl, N'-lower alkyl-ureido, N,N'-di-lower alkyl-ureido,

lower alkylsulfonylamino, nitro, lower alkenoyl,

and N-morpholino;

the word "lower" having the signification "up to C₆";

Y is C₁ to C₁₀ alkyl or AB

wherein

A is an alkyl chain from 1 to 10 carbons, branched or unbranched, and

B is a substituted or unsubstituted aryl or hetaryl group;



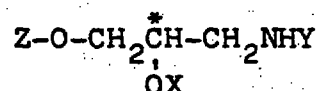
X is hydrogen or R-CO-
wherein

R is C₁-C₁₀ alkyl, phenyl, substituted phenyl,
or alkylphenyl;

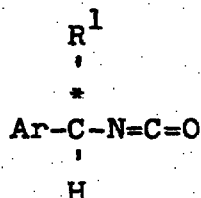
Ar represents an aryl group, for example
phenyl, substituted phenyl or naphthyl; and

R¹ is C₁-C₆ alkyl;

said process comprising reacting a compound of Formula I



wherein Z, Y and X are as previously defined with a
compound of Formula II



wherein Ar and R¹ are as previously defined so as to
produce a pair of diastereomeric urea derivatives of
Formula III and then separating said pair of
diastereomeric urea derivatives of Formula III;
said separating step being achieved by the use in the
said reacting step of a reaction liquid in which one
of said pair of diastereomeric urea derivatives of
Formula III is soluble and the other of said pair of
derivatives is insoluble.



* C L N S *

2. The process of claim 1 wherein Z is an ortho substituted phenyl ring.
3. The process of claim 1 wherein Z is an ortho substituted pyridine ring.
4. The process of claim 1, 2 or 3 wherein A is a C₂-C₄ alkyl chain, branched or unbranched, and B is an indole ring system.
5. The process of any of claims 1 to 4 wherein X is hydrogen.
6. The process of any of claims 1 to 5 wherein R¹ is methyl and Ar is 1-naphthyl.



7. The process of claim 1 wherein N-[3-(2-cyanophenoxy)-2-hydroxypropyl]-N-[1,1-dimethyl-2-(1H-indol-3-yl)ethyl]-N'-[1-(1-naphthyl)ethyl]urea diastereomers are produced and separated.
8. The process of any of claims 1 to 7 wherein the said reaction liquid is benzene.
9. The process of claim 1 substantially as described in respect of any of the foregoing Examples.
10. A urea derivative of the Formula III specified in claim 1 prepared by the process of any of claims 1 to 9.
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