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<p>(54) Title: SYNTHESIS OF 3-ARYL-1-INDANAMINES</p>		
<p>(I)</p>		
<p>(57) Abstract</p> <p>The present invention is a method of preparing a 3-aryl-1-indanamine represented by structural formula I and physiologically acceptable salts thereof. In structure I, phenyl ring A can be unsubstituted or substituted with 1-4 substituents. R¹ is an aromatic group which can be substituted or unsubstituted. R² and R³ are each, independently, hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, an aralkyl group, or a substituted aralkyl group. Alternatively R² and R³, taken together with the nitrogen substituent on the indan ring, form a non-aromatic ring system having 1-2 heteroatoms.</p>		

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SYNTHESIS OF 3-ARYL-1-INDANAMINES

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/070,934, filed on January 9, 1998, entitled "Synthesis of *Trans*-N,N-Dimethyl[3-(3',4'-Dichlorophenyl) Indan-1-yl] Ammonium Hydrogen Maleate," the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

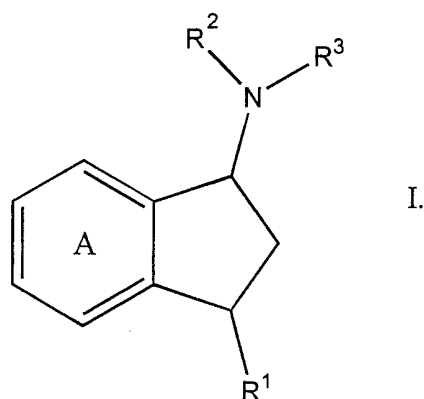
Biogenic amines derived from the amino acid tyrosine (dopamine, norepinephrine, and epinephrine) and tryptophan (serotonin) are neurotransmitters that have been shown to be involved in disorders such as psychosis, depression, and Parkinson's disease. Chemicals that modulate the activity of one or more of these neurotransmitters can be used to treat the symptoms of these disorders. *Trans*-3-aryl-1-indanamines have been shown to be potent inhibitors of dopamine, norepinephrine and epinephrine uptake, while *cis*-3-aryl-1-indanamines have been shown to selectively inhibit the uptake of serotonin (Bogeso, *et al.*, *J. Med. Chem.*, (1985), 28:1817).

Current synthetic routes to 3-aryl-1-indanamines produce a mixture of the regioisomers which must be separated. These methods typically are costly and time consuming.

SUMMARY OF THE INVENTION

The present invention is a method of preparing a 3-aryl-1-indanamine represented by structural formula I:

-2-



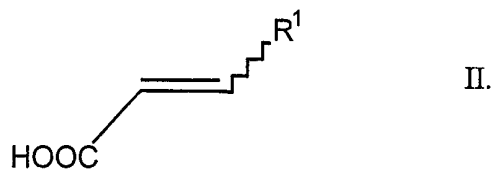
and physiologically acceptable salts thereof.

In structural formula I, phenyl ring A can be unsubstituted or substituted with 1-4 substituents.

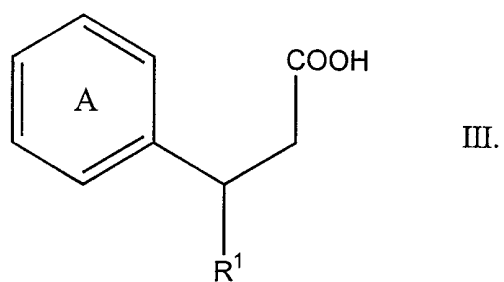
R^1 is an aromatic group which can be substituted or unsubstituted.

R^2 and R^3 are each, independently, hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, an aralkyl group, or a substituted aralkyl group. Alternatively, R^2 and R^3 , taken together with the nitrogen substituent on the indan ring, form a non-aromatic ring system having 1-2 heteroatoms such as nitrogen, oxygen or sulfur.

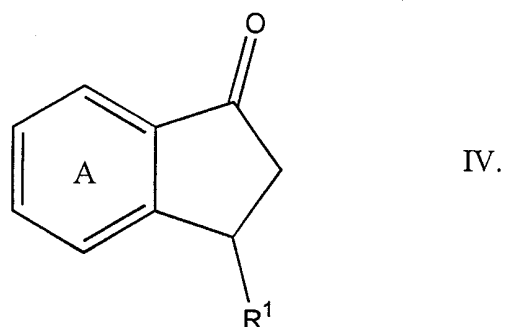
The method of preparing a 3-aryl-1-indanamine represented by structural formula I comprises a first step of reacting, in the presence of a Friedel-Crafts catalyst and a proton source, a substituted or unsubstituted benzene, having at least two consecutive unsubstituted aromatic carbons, with a 3-aryl-1-prop-2-enoic acid to form a 3-aryl-3-phenyl-1-propanoic acid. 3-Aryl-1-prop-2-enoic acid and 3-aryl-3-phenyl-1-propanoic acid can be represented by structural formulas II and III, respectively:



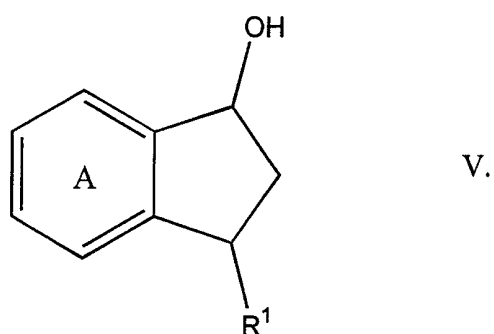
-3-



The method further comprises a second step in which the 3-aryl-3-phenyl-1-propanoic acid (III) formed in step 1 is treated with a second Friedel-Crafts catalyst to form a 3-arylindan-1-one represented by structural formula IV:

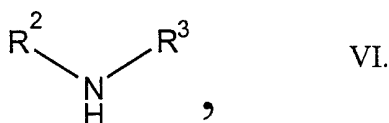


The method further comprises a third step in which the 3-arylindan-1-one (IV) formed in step 2 is reacted with a reducing agent to form a 3-arylindan-1-ol represented by structural formula V:



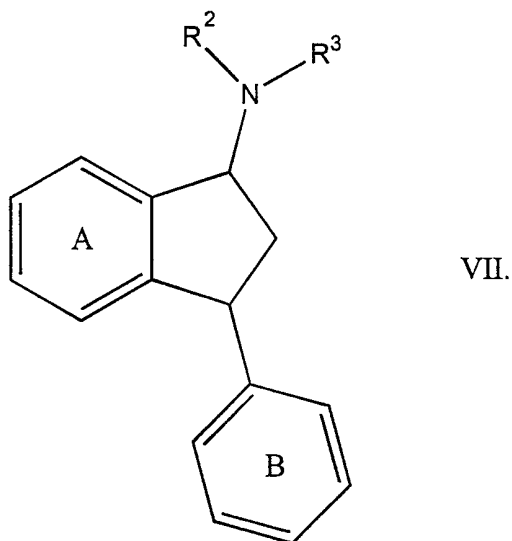
The method further comprises a fourth step in which the 3-arylidan-1-ol (V) formed in step 3 is reacted with an activating agent in the presence of a base to form an activated 3-arylidan-1-ol.

The method further comprises a fifth step in which the activated 3-arylidan-1-ol formed in step 4 is reacted with an amine compound represented by structural formula VI:



to form a 3-aryl-1-indanamine.

Another embodiment of the present invention is a method of forming a 3-phenyl-1-indanamine represented by structural formula VII:

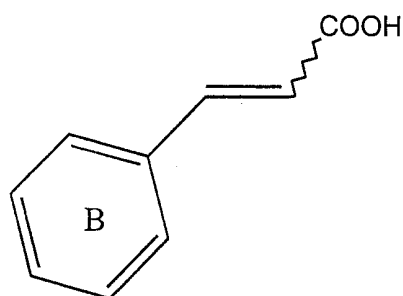


and physiologically acceptable salts thereof.

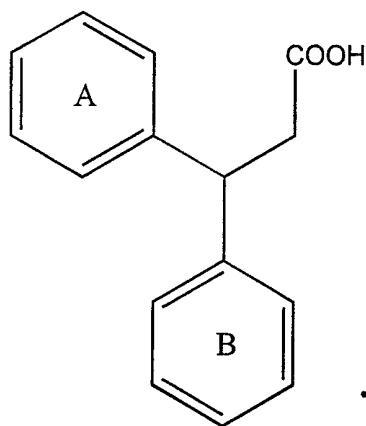
Rings A and B are each, independently, substituted or unsubstituted. Ring A can be unsubstituted or can have 1-4 substituents, and ring B can be unsubstituted or can have 1-5 substituents.

R² and R³ are defined as above.

The method of preparing a 3-phenyl-1-indanamine represented by structural formula VII comprises a first step of reacting, in the presence of sulfuric acid, a substituted or unsubstituted benzene, having at least two consecutive unsubstituted aromatic carbons, with a 3-phenyl-1-prop-2-enoic acid to form a 3,3-diphenyl-1-propanoic acid. 3-Phenyl-1-prop-2-enoic acid and 3,3-diphenyl-1-propanoic acid can be represented by structural formulas VIII and IX, respectively:



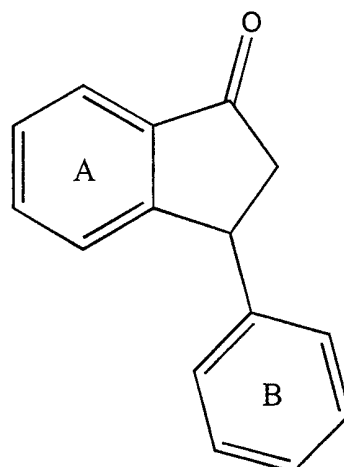
VIII.



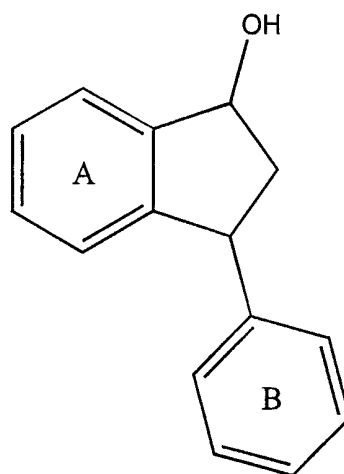
IX.

The method further comprises a second step of treating the 3,3-diphenyl-1-propanoic acid (IX) formed in step 1 with chlorosulfonic acid to form a 3-phenylindan-1-one represented by structural formula X:

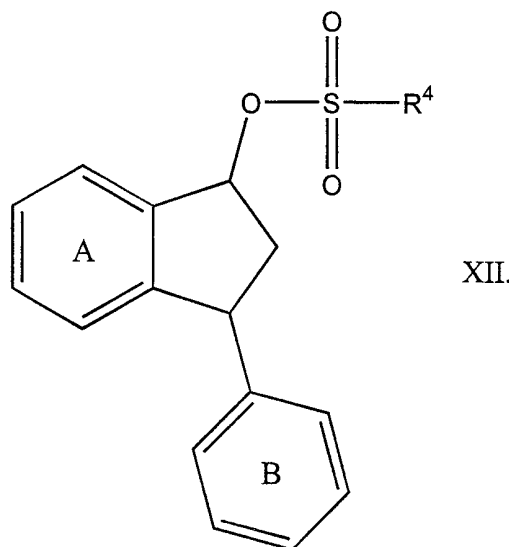
-6-



The method further comprises a third step of reacting the 3-phenylindan-1-one (X) formed in step 2 with sodium borohydride to form a 3-phenylindan-1-ol represented by structural formula XI:



The method further comprises a fourth step in which the 3-phenylindan-1-ol (XI) formed in step 3 is reacted with an aliphatic or aromatic sulfonyl chloride in the presence of a base to form a 3-phenylindan-1-sulfonate ester represented by structural formula XII:



wherein R^4 is a substituted or unsubstituted aliphatic or aromatic group.

The method further comprises a fifth step in which the 3-phenylindane-1-sulfonate ester (XII) formed in step 4 is reacted with an amine compound represented by structural formula VI to form the 3-phenyl-1-indanamine (VII).

Another embodiment of the present invention is a method of preparing a 3-phenyl indan-1-one represented by structural formula X. The method comprises a first step of reacting, in the presence of a first Friedel-Crafts catalyst and a proton source, a compound represented by structural formula VIII with a substituted or unsubstituted benzene having at least two consecutive unsubstituted aromatic carbons to form a 3,3-diphenyl-1-propanoic acid (IX), and a second step in which the 3,3-diphenyl-1-propanoic acid (IX) is converted to a 3-phenylindane-1-one (X) by treatment with a second Friedel-Crafts catalyst.

Another embodiment of the present invention is a method of preparing a 3-phenyl indan-1-ol represented by structural formula XI. The method comprises three reaction steps. In the first step, a compound represented by structural formula VIII is reacted, in the presence of a first Friedel-Crafts catalyst and a proton source, with a substituted or unsubstituted benzene having at least two consecutive unsubstituted aromatic carbons to form a 3,3-diphenyl-1-propanoic acid (IX). In the second step, the 3,3-diphenyl-1-propanoic acid (IX) is converted to a 3-phenylindane-1-one (X) by

treatment with a second Friedel-Crafts catalyst. In the third step, the 3-phenyl indan-1-one (X) is reacted with a reducing agent to form a 3-phenylindan-1-ol (XI).

Another embodiment of the present invention is a method of preparing a 3-phenylindan-1-one represented by structural formula X. The method comprises the step of treating a 3,3-diphenyl-1-propanoic acid (IX) with a Friedel-Crafts catalyst.

Another embodiment of the present invention is a method of preparing a 3-phenyl-1-indanamine represented by structural formula VII. The method comprises a first step in which a 3-phenylindan-1-ol (XI) is reacted with an activating agent in the presence of a base to form an activated 3-phenyl-1-indanamine, and a second step in which the activated 3-phenyl-1-indanamine is reacted with an amine compound represented by structural formula VI to form the 3-phenyl 1-indanamine (VII).

3-Aryl-1-indanamines are potent inhibitors of dopamine, norepinephrine, epinephrine and serotonin uptake, and therefore, expected to be useful in treating disorders such as psychosis, depression and Parkinson's disease. The method described herein allows 3-aryl-1-indanamines to be synthesized in high yields with fewer reaction steps than previously described methods. In addition, *trans*-3-aryl-1-indanamines can be selectively prepared by the method of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The features and other details of the method on the invention will now be more particularly described and pointed out in the claims. It will be understood that the particular embodiments of the invention are shown by way of illustration and not as limitations of the invention. The principle features of this invention can be employed in various embodiments without departing from the scope of the invention. All parts and percentages are by weight unless otherwise specified.

A schematic representation of the method of preparing a 3-aryl-1-indanamine can be seen in Scheme I. The first step is a Friedel-Crafts alkylation in which a benzene adds to a double bond. Dialkylation is minimized by using excess benzene. A proton source is necessary for the reaction, therefore protonic Friedel-Crafts catalysts are preferred. A proton source is a compound that has acidic protons, such as organic or

inorganic acids.

The second step is a Friedel-Crafts acylation to close the five membered ring. This reaction can proceed by converting the carboxylic acid into an acid chloride followed by treatment with a Lewis acid, or the carboxylic acid can be added directly to ring A by treatment with a protonic Friedel-Crafts catalyst.

A Friedel-Crafts catalyst can be a Lewis acid (i.e., an electron acceptor) or a protonic acid (i.e., a proton donor). Protonic acids are preferred for the Friedel-Crafts alkylation of step 1. Examples of protonic acid catalysts include inorganic acids such as anhydrous sulfuric acid or hydrogen fluoride. Examples of Lewis acids that can catalyze Friedel-Crafts alkylations and acylations include AlBr_3 , AlCl_3 , GaCl_3 , FeCl_3 , SbCl_5 , ZrCl_4 , SnCl_4 , BCl_3 , BF_3 , SbCl_3 .

In the third reaction step, the ketone is reacted with a reducing agent to form an alcohol. A reducing agent, as used herein, is a chemical or combination of chemicals that will convert the ketone to an alcohol. Suitable reducing agents include sodium borohydride, lithium borohydride, borane, disiamylborane, 9-bora-bicyclo[3.3.1]nonane, lithium tri-tert-butoxyaluminumhydride aluminum hydride, lithium triethylborohydride, and lithium tri(sec-butyl)borohydride. Preferred reducing agents selectively convert the 3-aryllindan-1-one into a *cis*-3-aryllindan-1-ol. Sodium borohydride is a preferred reducing agent.

Other reducing agents suitable for preferentially forming either *cis* or *trans* 3-aryllindan-1-ol include combinations of a carbonyl reducing agent, such as lithium aluminum hydride, lithium borohydride or sodium borohydride, with an optically pure compound, such as an amino alcohol, sugar or hydroxyalkaloid. Typically, a chiral reducing agent is about 25% to about 75% (w/w) carbonyl reducing agent and about 25% to about 75% (w/w) optically active compound. Other suitable reducing agents suitable for preferentially forming either a *cis* or *trans* 3-aryllindan-1-ol include 2,5-dimethylborolane, as described in Imai *et al.*, *J. Am. Chem. Soc.*, 108:7402 (1986), K-glucoride, as described in Brown *et al.*, *J. Org. Chem.*, 53:1231 (1988), NB-Enantride, as described in Midland *et al.*, *J. Org. Chem.*, 56:1068 (1991), borane with a chiral oxazaborolidine catalyst, as described in Corey *et al.*, *J. Am. Chem. Soc.*, 109:7925

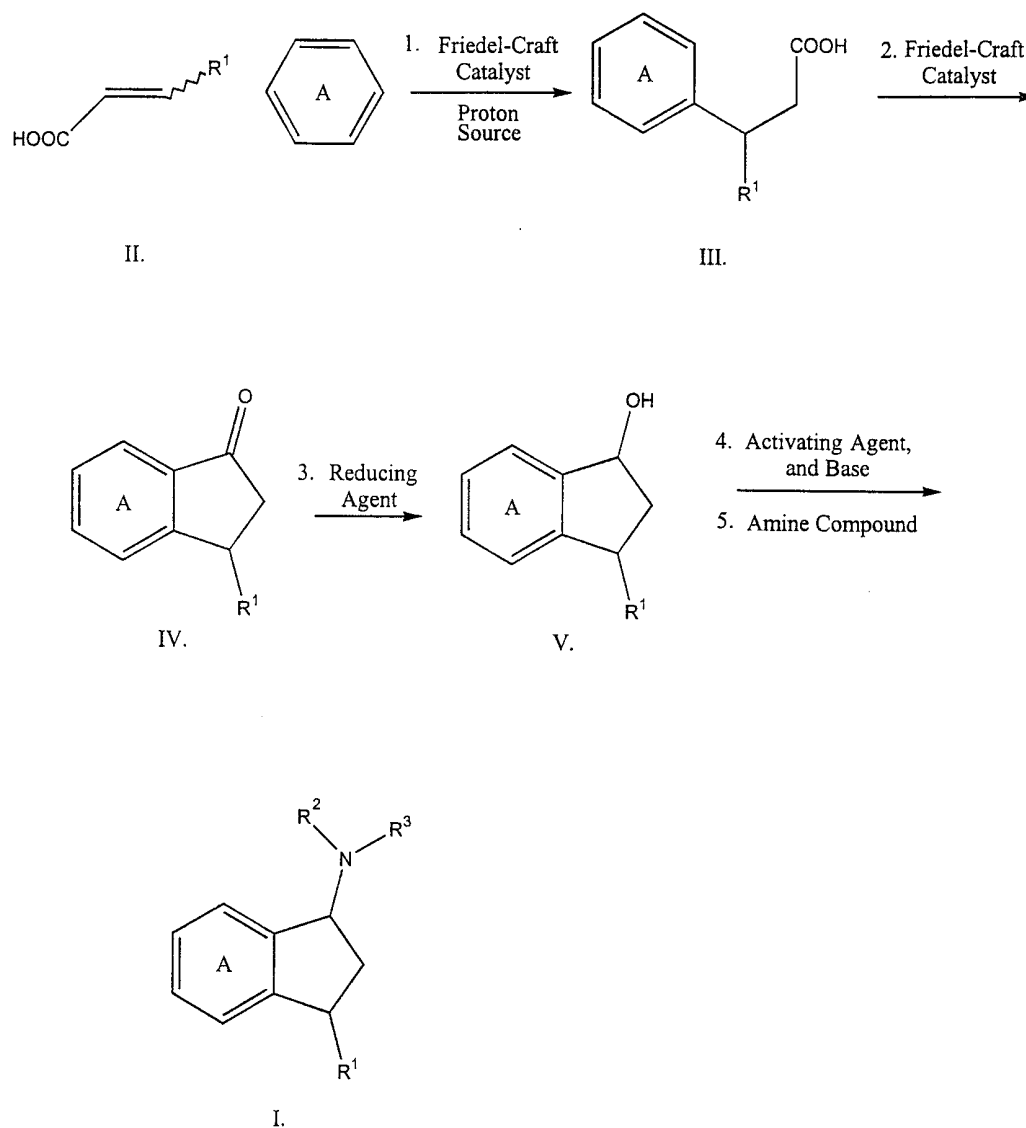
(1987), and R-Alpine-Hydrate and S-Alpine-Hydrate, obtainable from Aldrich Chemical Co.

Alternatively, preferential formation of a *cis* or *trans* 3-arylindan-1-ol can occur through the use of a sterically large (or bulky) carbonyl agent.

In the fourth step, the 3-arylindan-1-ol is reacted with an activating agent. An activating agent, as used herein, is a compound that can react with an alcohol in the presence of a base to convert the alcohol into a good leaving group. Suitable activating agents include thionyl chloride or substituted or unsubstituted aliphatic or aromatic sulfonyl chlorides, for example, trifluoromethanesulfonyl chloride. Suitable bases include hindered organic bases such as trialkyl amines. Preferred activating groups can react with the 3-arylindan-1-ol such that it retains its chiral configuration at the C-1 position. A particularly preferred activating agent and base combination is a substituted or unsubstituted aliphatic or aromatic sulfonyl chloride and a trialkyl amine.

In the fifth step, an amine compound is reacted with the activated 3-arylindan-1-ol. An amine compound, as used herein, is ammonia or a compound that has a primary or secondary amine. The amine can be part of a ring system. For example, piperazine, pyrrolidine, piperidine, morpholine and piperidinopiperidine. Amine compounds that react with the activated 3-arylindan-1-ol and invert the chiral configuration at the C-1 position are preferred. For example, an amine compound that reacts with an activated *cis*-3-arylindan-1-ol to form a *trans*-3-aryl-1-indanamine is preferred. Piperazines are particularly preferred amine compounds.

The 3-aryl-1-indanamine is obtained as the free base which can be converted to a salt by recrystallization with an acid such as maleic acid. Physiologically acceptable salts are preferred. An enantiomerically pure chiral acid, such as L-(+) or D-(-) tartaric acid, can be used to resolve the (1S, 3R) and (1R, 3S) enantiomers of 3-aryl-1-indanamine by selective recrystallization of the salt. The salt can be converted back to the free base by treating with a basic solution, such as an aqueous sodium bicarbonate solution, followed by extraction of the enantiomerically pure 3-aryl-1-indanamine with an organic solvent.



Scheme I: Synthesis of 3-aryl-1-indanamine.

Aliphatic groups, as used herein, include straight chained or branched C_1 - C_{18} hydrocarbons which are completely saturated or which contain one or more units of unsaturation, or cyclic C_3 - C_{18} hydrocarbons which are completely saturated or which contain one or more unconjugated double bonds. Lower alkyl groups are straight chained or branched C_1 - C_6 hydrocarbons or C_3 - C_6 cyclic hydrocarbons which are completely saturated.

Aromatic groups include carbocyclic ring systems (e.g. benzyl) and fused polycyclic, carbocyclic ring systems (e.g. naphthyl, anthracenyl or 1,2,3,4-tetrahydronaphthyl). In addition, aromatic groups include heteroaryl ring systems (e.g., thiophene, furan, pyrroles, or pyrans) and heteroaryl ring systems in which a carbocyclic aromatic ring, a carbocyclic non-aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. For example, benzimidazole, thianaphthene, benzofuran, or indole. An aryl group is a carbocyclic aromatic ring system or a polycyclic, carbocyclic aromatic ring system.

An aralkyl group is an aromatic substituent that is linked to a compound by an aliphatic group having from one to four carbon atoms.

Suitable substituents include aliphatic groups, halogenated aliphatic groups, aromatic groups, aralkyl groups, halogens, trihalomethyl, cyano, and nitro. Other suitable substituents include R^6O- , $R^6OC(O)-$, $R^6C(O)-$, $R^6C(O)O-$, R^6S- , $R^6S(O)-$, $R^6S(O)_2-$, $R^6S(O)_2O-$, R^6R^7N- , $R^6R^7NC(O)-$, $R^6HNC(O)NH-$, or $R^6C(O)NH-$, wherein R^6 and R^7 are each, independently, hydrogen, a lower alkyl group, an aryl group and an aralkyl group.

In a preferred embodiment, ring A is substituted with one to four activating substituents. An activating substituent is a substituent that is an electron donor, and therefore, increases the electron density of the aromatic ring. Examples of activating substituents include aliphatic groups, aromatic groups, aralkyl groups, R^6O- , and R^6S- .

In another preferred embodiment, the aromatic group represented by R^1 is substituted with a deactivating substituent. A deactivating substituent is an electron withdrawing substituent. Electron withdrawing substituents decrease the electron density of the aromatic ring. Examples of deactivating substituents include halogens, trihalomethyl, cyano, nitro, $R^6OC(O)-$, $R^6C(O)-$, $R^6S(O)-$, $R^6S(O)_2-$ and $R^6R^7NC(O)-$.

In another preferred embodiment, ring B is substituted with a deactivating substituent.

EXEMPLIFICATION

Example 1 - Synthesis of 3-(3',4'-Dichlorophenyl) 3-Phenylpropanoic Acid

A mixture of 3,4-dichlorocinnamic acid (50 g, 0.23 mole), benzene (150 mL) and concentrated sulfuric acid (100 mL) was stirred (using air driven overhead stirrer) in a 500 mL 3-neck round bottom flask while maintaining a reaction temperature of 85-95°C. The progress of the reaction was followed by HPLC. When the level of 3,4-dichlorocinnamic acid was $\leq 1\%$ by HPLC (approximately 24 h), the reaction mixture was cooled to room temperature, then slowly poured into ice (300 g). The mixture was stirred for 30 min. then transferred into a 2 L separatory funnel. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with ethyl acetate (2 x 300 mL). The organic layers were combined, washed with water (5 x 500 mL) and brine (2 x 400 mL), then concentrated under reduced pressure. Ethyl acetate (500 mL) was added to the concentrate and the solution was evaporated to dryness. The product was dried under high vacuum at room temperature for 24 h. The desired carboxylic acid was obtained as a thick oil (65.8 g, 96% yield).

Example 2 - Synthesis of 3-(3',4'-Dichlorophenyl) Indan-1-one

Chlorosulfonic acid (66 mL, 0.99 mole) was added slowly to a stirring solution of 3-(3',4'-dichlorophenyl) 3-phenylpropanoic acid (65 g, 0.22 mole) in dichloromethane (330 mL) at room temperature. After 30 min., the reaction was monitored by TLC against authentic sample of 3-(3',4'-dichlorophenyl) 3-phenylpropanoic acid. If the reaction was not complete, an additional 10-20 mL of chlorosulfonic acid was added and the reaction was stirred for an additional 30 min. When the reaction was complete, the mixture was slowly poured into ice (400 g), stirred for 15 min., then transferred to a 1 L separatory funnel. The organic layer was drained and the aqueous layer was extracted with ethyl acetate (2 x 400 mL). The combined organic layers were washed with water (5 x 500 mL) and brine (2 x 400 mL), then concentrated under reduced pressure. A mixture of ethyl acetate : heptane (1 : 9) (100 mL) was added to the concentrate and the solution was stirred for one hour at room

temperature. The temperature was lowered to 5-10°C and stirring was continued for 4 hours. The precipitate was recovered by filtration and washed with a cold solution (2 x 100 mL) of 1 : 9 ethyl acetate : heptane. The off-white solid was dried under high vacuum for 16 h to obtain 45.6 g (71%) of product. The 3-(3',4'-dichlorophenyl)indan-1-one was 97% pure by HPLC.

Example 3 - Synthesis of *Cis*-3-(3',4'-Dichlorophenyl)indan-1-ol

A solution of 3-(3',4'-dichlorophenyl)indan-1-one (25 g, 0.09 mole) in 250 mL of tetrahydrofuran (hereinafter "THF") was stirred at -5°C. In a separate flask, a solution of sodium borohydride (6.8 g, 0.18 mole) in water (28 mL) was cooled to 0°C, then added dropwise to the solution of 3-(3',4'-dichlorophenyl)indan-1-one, maintaining the temperature of the reaction mixture between -5 - 0°C. After addition of the sodium borohydride solution was complete, the cooling bath was removed and the reaction mixture was stirred for 2 h. The reaction was monitored by TLC against an authentic sample of *cis*-3-(3',4'-dichlorophenyl)indan-1-ol and an authentic sample of 3-(3',4'-dichlorophenyl)indan-1-one. When the starting material disappeared, 150 mL of ice-cold water was added to quench the reaction. After stirring for 1 h, THF was removed under reduced pressure, and the mixture was extracted with ethyl acetate (2 x 300 mL). The ethyl acetate layer was washed with water (2 x 250 mL) and brine (2 x 200 mL), then concentrated under reduced pressure to obtain an oily product. A solution (100 mL) of 1 : 9 ethyl acetate : heptane was added to the concentrate and stirred for 1 h at room temperature, then at 5 - 10°C for 4 h. The precipitated product was collected by filtration, then washed with an ice-cold solution (120 mL) of 1 : 9 ethyl acetate : heptane. After drying the solid under high vacuum for 12 h, 18.8 g (74%) of 98.5% pure alcohol was obtained. The product contained ≤ 1% of the undesired *trans*-alcohol.

Example 4 - Synthesis of *Trans*-1-(N,N-Dimethylamino) 3-(3',4'-Dichlorophenyl)indan

A solution of *cis*-3-(3',4'-dichlorophenyl)indan-1-ol (22.7 g, 0.081 mol) and triethylamine (45 mL, 0.325 mole) in THF (350 mL) was stirred (overhead stirring)

under an inert atmosphere while maintaining a solution temperature of -15°C . In a separate flask under inert atmosphere, a solution of methanesulfonyl chloride (12.6 mL, 0.162 mol) in the THF (150 mL) was cooled to -60°C , then added slowly to the solution of *cis*-3-(3',4'-dichlorophenyl) indan-1-ol, maintaining the temperature of the reaction mixture below 0°C . After addition was complete, the reaction mixture was stirred for 10 min. at 0°C , then purged with dimethylamine gas (56 g, 1.21 mol). The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was monitored by TLC against an authentic sample of *cis*-3-(3',4'-dichlorophenyl)indan-1-ol and against an authentic sample of *trans*-1-(N,N-dimethylamino) 3-(3',4'-dichlorophenyl)indan. When the reaction was complete, THF was removed under reduced pressure, and the mixture was extracted with ethyl acetate (250 mL). The ethyl acetate layer was removed, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate layers were washed with brine (2 x 100 mL) and dried over anhydrous sodium sulfate. The ethyl acetate solution was concentrated to give 26 g of 1-(N,N-dimethylamino)-3-(3',4'-dichlorophenyl)indan as a brown oil. The *cis* : *trans* isomeric ratio of the crude amine was 5 : 95 as determined by HPLC. The crude amine (26 g) was stirred with ethyl acetate (5 mL) for 10 min. After a solid started to form, heptane (45 mL) was added. The mixture was stirred for 1 hour at 15°C , then the precipitated product was collected by filtration, then washed with 40 mL of heptane. The product was dried under high vacuum to give 14 g of product (56%, first crop). The mother liquor was evaporated to an oil. A solution (15 mL) of 10% ethyl acetate in heptane was added to the oil and stirred for 1 hour at 15°C . The precipitated product was collected by filtration, then washed with 20 mL of heptane. The solid was dried under vacuum to give 5.2 g (21%, second crop). HPLC analysis indicated that the two crops contained the same ratio (0.6%) of the undesired *cis* isomer. The combined crops (19.2 g) were again stirred with a solution (40 mL) of 10% ethyl acetate in heptane for 1 hour at 15°C . The precipitated product was collected by filtration, then washed with 30 mL of heptane. The product was dried under high vacuum to give 15 g (60%) of 1-(N,N-dimethylamino) 3-(3',4'-dichlorophenyl) indan. Only 0.2% of the undesired *cis* isomer was detected by HPLC.

Example 5 - Synthesis of *Trans*-N,N-Dimethyl [3-(3',4'-Dichlorophenyl)indan-1-yl]
Ammonium Hydrogen Maleate

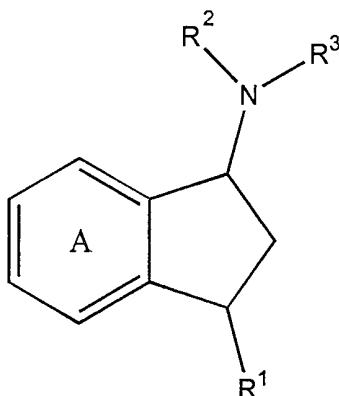
Trans-1-(N,N-dimethylamino)-3-(3',4'-dichlorophenyl)indan (13 g, 0.042 mole) was dissolved in ethanol (60 mL) at 50°C. In a separate flask, maleic acid (4.95 g, 0.042 mol) was dissolved in 20 mL of ethanol at 50°C, then added to the solution of *trans*-1-(N,N-dimethylamino)-3-(3',4'-dichlorophenyl)indan. The mixture was stirred at 50°C for 1 h, then at 10°C for 2 h. The precipitated product was collected by filtration, then washed with cold ethyl acetate (40 mL). The solid was dried under high vacuum to give 13.8 g (77%) of N,N-dimethyl [3-(3',4'-dichlorophenyl) indan-1-yl] ammonium hydrogen maleate. The ratio of the undesired *cis* isomer was 0.3% as detected by HPLC.

The N,N-dimethyl [3-(3',4'-dichlorophenyl) indan-1-yl] ammonium hydrogen maleate salt was converted back to the free base by stirring it in an aqueous NaHCO₃ solution, then extracting 1-(N,N-dimethylamino)-3-(3',4'-dichlorophenyl)indan with ethyl acetate.

CLAIMS

What is claimed is:

1. A method of preparing a 3-aryl-1-indanamine represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

ring A is substituted or unsubstituted;

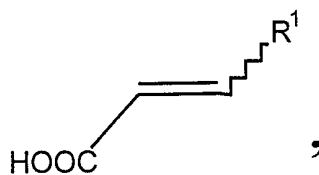
R¹ is a substituted or unsubstituted aromatic group;

R² and R³ are each, independently, hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, an aralkyl group, a substituted aralkyl group, or

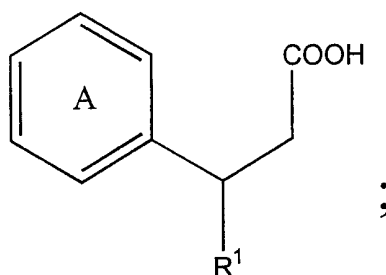
R² and R³, taken together with nitrogen, form a non-aromatic ring system having 1-2 heteroatoms, said method comprising the steps of:

- a) reacting, in the presence of a first Friedel-Crafts catalyst and a proton source, a substituted or unsubstituted benzene having at least two consecutive unsubstituted aromatic carbons, and a starting material represented by the following structural formula:

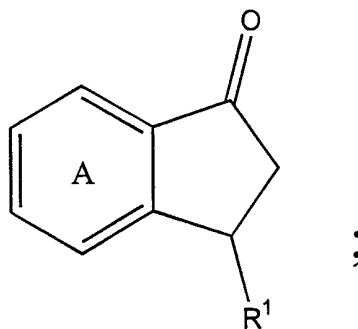
-18-



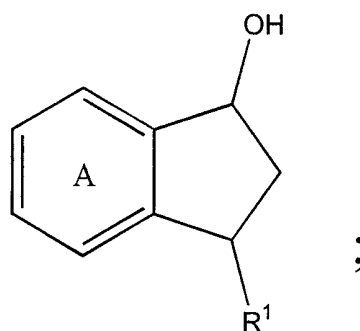
thereby forming a 3-aryl-3-phenyl-1-propanoic acid represented by the following structural formula:



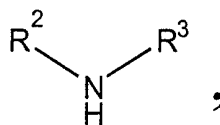
- b) contacting said 3-aryl-3-phenyl-1-propanoic acid with a second Friedel-Crafts catalyst, thereby forming a 3-arylindan-1-one represented by the following structural formula:



- c) reacting said 3-arylindan-1-one with a reducing agent, thereby forming a 3-arylindan-1-ol represented by the following structural formula:



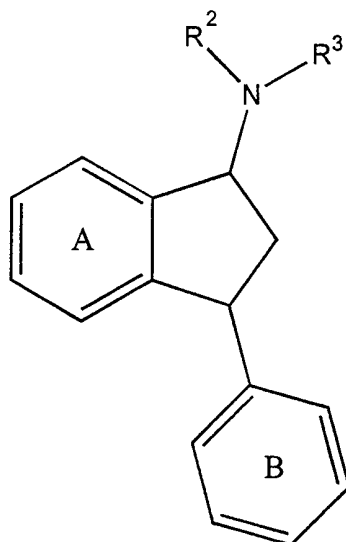
- d) reacting said 3-arylindanol with an activating agent in the presence of a base, thereby forming an activated 3-arylindanol; and
- e) reacting said activated 3-arylindanol with an amine compound represented by the following structural formula:



thereby forming said 3-aryl-1-indanamine.

2. The method of Claim 1, wherein said 3-aryl-1-indanamine has a *trans* configuration.
3. The method of Claim 2, wherein R¹ is a substituted or unsubstituted phenyl.
4. The method of Claim 3, wherein said phenyl is substituted with 1 to 5 deactivating substituents.
5. The method of Claim 4, wherein the deactivating substituents are 3'-chloro and 4'-chloro groups.

6. The method of Claim 1, wherein ring A is substituted with 1 to 4 activating substituents.
7. The method of Claim 1, wherein the first Friedel-Crafts catalyst is also the proton source.
8. The method of Claim 7, wherein said first Friedel-Crafts catalyst is an inorganic acid.
9. The method of Claim 8, wherein:
 - a) the inorganic acid is sulfuric acid;
 - b) the second Friedel-Crafts catalyst is chlorosulfonic acid;
 - c) the reducing agent is sodium borohydride;
 - d) the activating agent is a substituted or unsubstituted aliphatic or aromatic sulfonyl chloride; and
 - e) the amine compound is dimethyl amine.
10. A method of preparing a 3-phenyl-1-indanamine represented by the following structural formula:



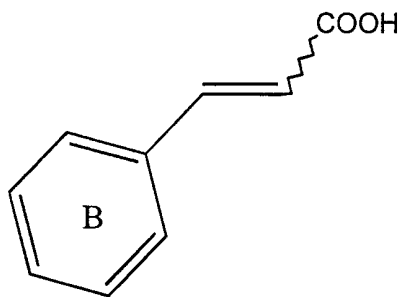
and physiologically acceptable salts thereof, wherein:

rings A and B are substituted or unsubstituted; and

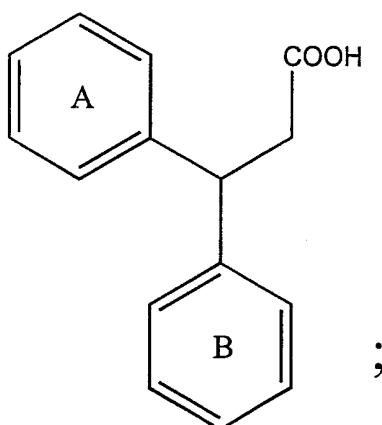
R^2 and R^3 are each, independently, hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, an aralkyl group, a substituted aralkyl group, or

R^2 and R^3 , taken together with nitrogen, form a non-aromatic ring system having 1-2 heteroatoms, said method comprising the steps of:

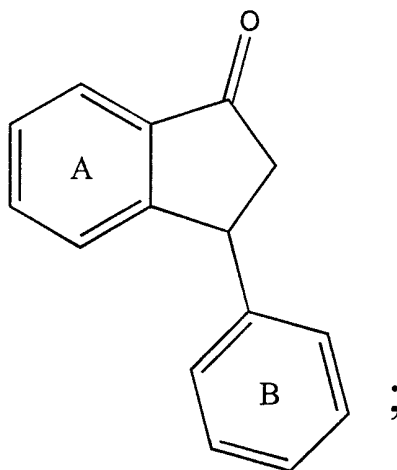
- a) reacting, in the presence of sulfuric acid, a substituted or unsubstituted benzene having at least two consecutive unsubstituted aromatic carbons, and a starting material represented by the following structural formula:



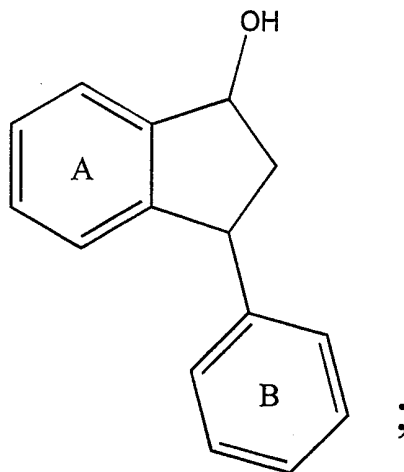
thereby forming a 3,3-diphenyl-1-propanoic acid represented by the following structural formula:



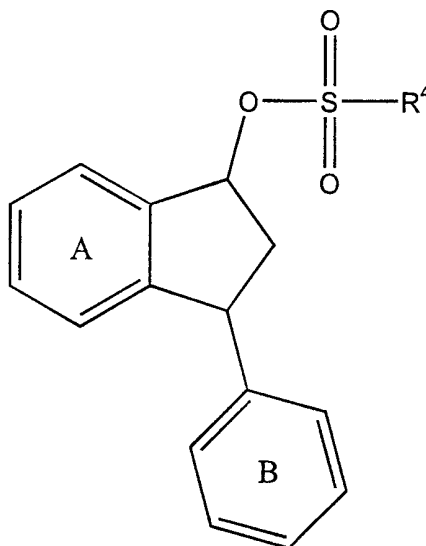
- b) contacting said 3,3-diphenyl-1-propanoic acid with chlorosulfonic acid, thereby forming a 3-phenylindan-1-one represented by the following structural formula:



- c) reacting said 3-phenylindan-1-one with sodium borohydride, thereby forming a 3-phenylindan-1-ol represented by the following structural formula:

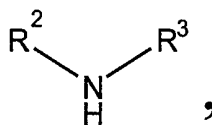


- d) reacting said 3-phenylindan-1-ol with substituted or unsubstituted aliphatic or aromatic sulfonyl chloride in the presence of a base, thereby forming a 3-phenylindan-1-sulfonate ester represented by the following structural formula:



wherein R^4 is a substituted or unsubstituted aliphatic or aromatic group;
and

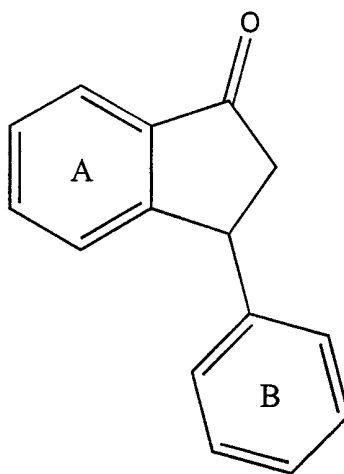
- e) reacting said 3-phenylindan-1-sulfonyl ester with an amine compound represented by the following structural formula:



thereby forming said 3-phenyl-1-indanamine.

11. The method of Claim 10, wherein said 3-phenyl-1-indanamine has a *trans* configuration.

12. The method of Claim 11, wherein ring B is substituted with 1 to 5 deactivating substituents.
13. The method of Claim 12, wherein the deactivating substituents are 3'-chloro and 4'-chloro groups.
14. The method of Claim 11, wherein ring A is substituted with 1 to 4 activating substituents.
15. The method of Claim 11 further comprising the step of:
 - f) contacting said *trans*-3-phenyl-1-indanamine with an acid, thereby forming a *trans*-3-phenyl-1-indanamine salt.
16. A method of preparing a 3-phenylindan-1-one represented by the following structural formula:

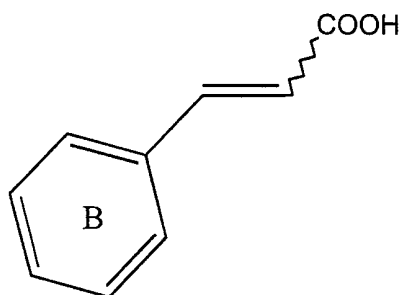


wherein:

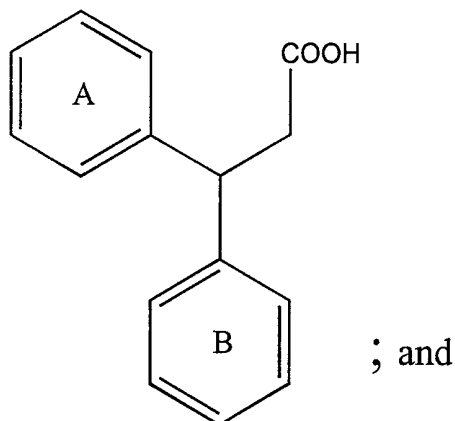
rings A and B are substituted or unsubstituted, said method comprising the steps of:

- a) reacting, in the presence of a first Friedel-Crafts catalyst and a proton source, a substituted or unsubstituted benzene having at least two

consecutive unsubstituted aromatic carbons, and a starting material represented by the following structural formula:

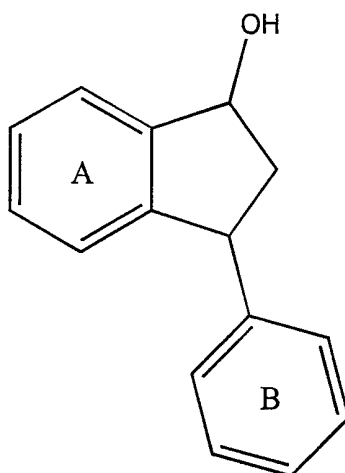


thereby forming a 3,3-diphenyl-1-propanoic acid represented by the following structural formula:



- b) contacting said 3,3-diphenyl-1-propanoic acid with a second Friedel-Crafts catalyst thereby forming said 3-phenylindan-1-one.
17. The method of Claim 16, wherein ring B is substituted with 1 to 5 deactivating substituents.
18. The method of Claim 17, wherein the deactivating substituents are 3'-chloro and 4'-chloro groups.

19. The method of Claim 16, wherein ring A is substituted with 1 to 4 activating substituents.
20. The method of Claim 16, wherein the first Friedel-Crafts catalyst is also the proton source.
21. The method of Claim 20, wherein said first Friedel-Crafts catalyst is an inorganic acid.
22. The method of Claim 21, wherein:
- a) the inorganic acid is sulfuric acid; and
 - b) the second Friedel-Crafts catalyst is chlorosulfonic acid.
23. A method of preparing a 3-phenylindan-1-ol represented by the following structural formula:

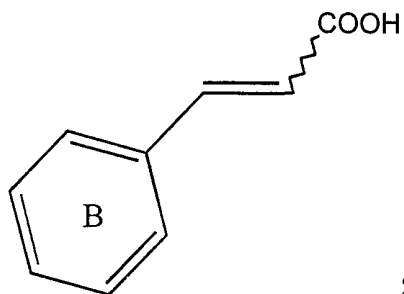


wherein:

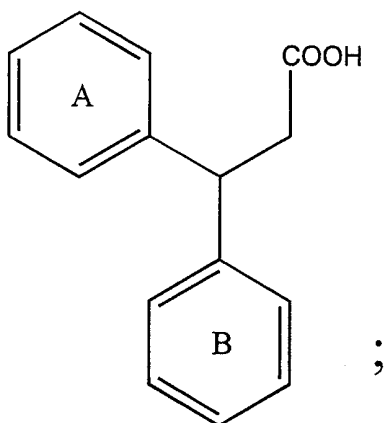
rings A and B are substituted or unsubstituted, said method comprising the steps of:

- a) reacting, in the presence of a first Friedel-Crafts catalyst and a proton source, a substituted or unsubstituted benzene having at least two

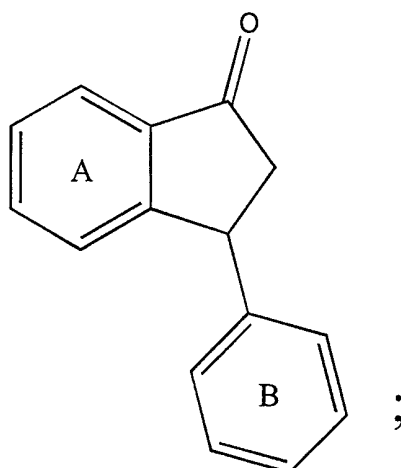
consecutive unsubstituted aromatic carbons, and a starting material represented by the following structural formula:



thereby forming a 3,3-diphenyl-1-propanoic acid represented by the following structural formula:

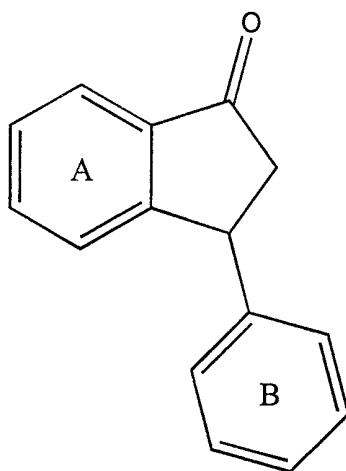


- b) contacting said 3,3-diphenyl-1-propanoic acid with a second Friedel-Crafts catalyst, thereby forming a 3-phenylindan-1-one represented by the following structural formula:



- c) reacting said 3-phenylindan-1-one with a reducing agent, thereby forming said 3-phenylindan-1-ol.
24. The method of Claim 23, wherein said 3-phenylindan-1-ol has a *cis* configuration.
25. The method of Claim 24, wherein ring B is substituted with 1 to 5 deactivating substituents.
26. The method of Claim 25, wherein the deactivating substituents are 3'-chloro and 4'-chloro groups.
27. The method of Claim 24, wherein ring A is substituted with 1 to 4 activating substituents.
28. The method of Claim 23, wherein the first Friedel-Crafts catalyst is also the proton source.
29. The method of Claim 28, wherein said first Friedel-Crafts catalyst is an inorganic acid.

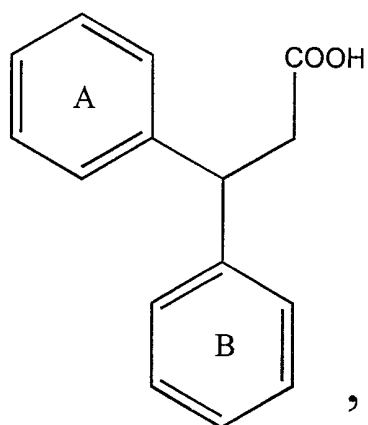
30. The method of Claim 29, wherein:
- the inorganic acid is sulfuric acid;
 - the second Friedel-Crafts catalyst is chlorosulfonic acid; and
 - the reducing agent is sodium borohydride.
31. A method of preparing a 3-phenylindan-1-one represented by the following structural formula:



wherein:

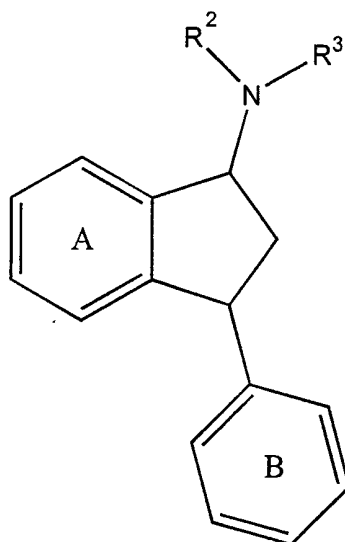
rings A and B are substituted or unsubstituted,

comprising the step of contacting with a Friedel-Crafts catalyst a compound represented by the following structural formula:



thereby forming a 3-phenylindan-1-one.

32. The method of Claim 31, wherein the Friedel-Crafts catalyst is chlorosulfonic acid.
33. A method of preparing a 3-phenyl-1-indanamine represented by the following structural formula:



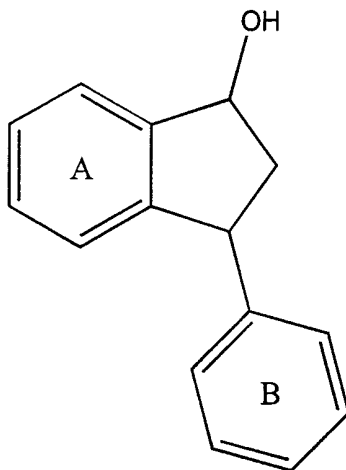
and physiologically acceptable salts thereof, wherein:

rings A and B are substituted or unsubstituted; and

R^2 and R^3 are each, independently, hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, an aralkyl group, a substituted aralkyl group, or

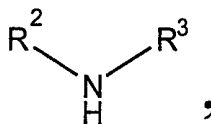
R^2 and R^3 , taken together with nitrogen, form a non-aromatic ring system having 1-2 heteroatoms, said method comprising the steps of:

- a) reacting a 3-phenylindan-1-ol represented by the following structural formula



with an activating agent in the presence of a base, thereby forming an activated 3-phenylindan-1-ol; and

- b) reacting said activated 3-phenylindan-1-ol with an amine compound represented by the following structural formula:



thereby forming said 3-phenyl-1-indanamine.

34. The method of Claim 33, wherein the 3-phenylindan-1-ol has a *cis* conformation.
35. The method of Claim 34, wherein the activating agent is an substituted or unsubstituted aliphatic or aromatic sulfonyl chloride.
36. The method of Claim 35, wherein the activated 3-phenylindan-1-ol has a *cis* configuration.
37. The method of Claim 36, wherein the 3-phenyl-1-indanamine has a *trans* configuration.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00225

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C209/16 C07C51/353 C07C45/46 C07C29/143

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 23 39 715 A (HOECHST AG) 27 February 1975 see page 10, paragraph 7 - page 11, paragraph 1; claim 1 ---	1-37
Y	DIETMAR KUCK ET AL.: "Synthesis of tribenzotriquinacene..." CHEMISCHE BERICHTE., vol. 127, no. 1, January 1994, pages 151-164, XP002098218 WEINHEIM DE see page 152, column 1 ---	1-37
	-/--	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents:

- "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 when the document is taken alone
- "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

Date of the actual completion of the international search

29 March 1999

Date of mailing of the international search report

13/04/1999

Name and mailing address of the ISA

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Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00225

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CHEMICAL ABSTRACTS, vol. 33, no. 15, 10 August 1939 Columbus, Ohio, US; abstract no. 6258, J. H. SIMONS AND AL.: "Hydrogen fluoride as a condensing agent..." page 6257; column 2; XP002098219 see abstract & JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 61, 1939, pages 1521-1522, DC US</p> <p style="text-align: center;">---</p>	1-37
Y	<p>BOGESO K P ET AL: "3-PHENYL-1-INDANAMINES, POTENTIAL ANTIDEPRESSANT ACTIVITY AND POTENT INHIBITION OF DOPAMINE, NOREPINEPHRINE AND SEROTONIN UPTAKE" JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 12, 1985, pages 1817-1828, XP002047150 cited in the application see page 1819, column 2, paragraph 3 to page 1820, Scheme 1 and page 1827, paragraph 3</p> <p style="text-align: center;">---</p>	1-37
Y	<p>EP 0 076 669 A (KEFALAS AS) 13 April 1983 see page 7; example 1</p> <p style="text-align: center;">---</p>	1-37
Y	<p>EP 0 035 363 A (KEFALAS AS) 9 September 1981 see page 8-9; example 8</p> <p style="text-align: center;">-----</p>	1-37

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/00225

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
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, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

SEE ADDITIONAL SHEET

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. 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 claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/00225

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
DE 2339715	A	27-02-1975	NONE	
<hr style="border-top: 1px dashed black;"/>				
EP 0076669	A	13-04-1983	AU 8898282 A	14-04-1983
			DK 438482 A	06-04-1983
			FI 823360 A	06-04-1983
			GR 76712 A	29-08-1984
			JP 58077846 A	11-05-1983
			PT 75636 A,B	01-11-1982
			ZA 8206924 A	31-08-1983
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EP 0035363	A	09-09-1981	AT 13056 T	15-05-1985
			AU 538424 B	16-08-1984
			AU 6791781 A	16-09-1982
			CA 1181750 A	29-01-1985
			DK 92781 A,B,	30-08-1981
			FI 810604 A,B,	30-08-1981
			GB 2071088 A,B	16-09-1981
			IE 50867 B	06-08-1986
			JP 1600624 C	31-01-1991
			JP 2024819 B	30-05-1990
			JP 56167670 A	23-12-1981
			US 4443448 A	17-04-1984
			ZA 8101223 A	28-04-1982
<hr style="border-top: 1px dashed black;"/>				