

Description

This invention relates to the field of pharmaceutical chemistry and involves a crystalline salt of a substituted tetrahydrobenz[cd]indole and its use.

Flaugh in U.S. Patent No. 4,576,959 discloses that 6-substituted-4-dialkylaminotetrahydrobenz[c,d]-indoles and their pharmaceutically acceptable salts are central serotonin agonists, useful for treating depression, obesity, alcoholism, smoking, or senile dementia. Leander in U.S. Patent No. 4,745,126 further discloses that certain 4-dialkylamino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[c,d]indoles and their pharmaceutically acceptable acid addition salts are useful in treating anxiety.

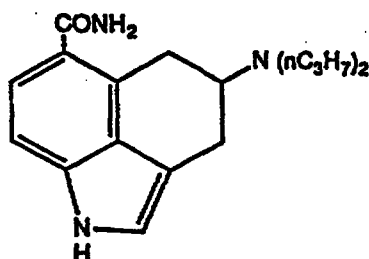
It is recognized in the art that it is particularly advantageous that a solid pharmaceutical substance be crystalline, rather than amorphous. Typically, crystalline solids more easily purified, more easily characterized, and more pharmaceutically elegant than solids which are amorphous. This invention provides a crystalline acid addition salt of a particularly preferred compound of Flaugh and of Leander.

Summary of the Invention

This invention provides 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate. In a further embodiment the invention involves substantially (4S)- or (4R)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate. In another embodiment, this invention involves a pharmaceutical formulation comprising at least one of said compounds together with a pharmaceutical excipient, diluent, or carrier therefor. Another embodiment of this invention concerns a method for treating conditions in a mammal requiring modification of serotonin function in the body by administering an amount of said compound sufficient to affect serotonin function. Another embodiment of the present invention concerns a method of treating depression in humans comprising administering to a depressed individual an antidepressant dose of said compound. A further embodiment of this invention concerns a method of treating anxiety in humans comprising administering to a human susceptible to or suffering from anxiety an antianxiety dose of said compound. In another embodiment the present invention involves a method for preparing the crystalline hippurate by dissolving the indole and hippuric acid in a solvent and then crystallizing the hippurate. In a still further embodiment the indole and hippurate are contacted in a mixture of isopropyl alcohol and water.

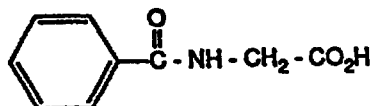
Detailed Description of the Invention

All temperatures discussed herein are expressed in degrees Celsius. The term "substantially" is used herein to mean that at least 95 weight percent of the designated material is present. The base compound is ($\pm$)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole, which has the structure:



(I)

The acid addition salt of this invention is formed by contacting the base compound of Formula I with hippuric acid, also known as N-benzoylglycine and also known as benzamidoacetic acid, which has the structure:



(II)

The acid addition salt is, therefore, 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]-indole hippurate. The salt corresponds to a one to one molar ratio of the indole to hippuric acid.

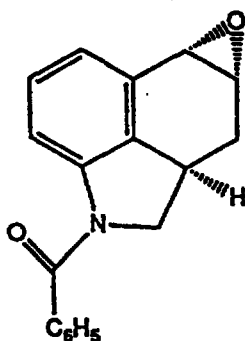
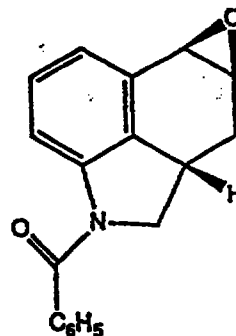
The hippurate salt of the compound of Formula I has the particularly advantageous property of crystallinity, unlike numerous other acid addition salts of Formula I that have been prepared. As a crystalline substance, the hippurate salt can be readily prepared in high purity by dissolving the base compound (indole) in an inert solvent or mixture of inert solvents, adding hippuric acid, and allowing the thus formed salt to crystallize. The solvent of choice should be capable of dissolving the hippuric acid and indole but should not chemically react with either. The solvent should have a low solubility for the hippurate salt. Preferably the solvent also has a low toxicity level. Solvents include isopropyl alcohol, acetone, ethanol, isopropyl alcohol and water mixture, methyl ethyl ketone, butanol, tetrahydrofuran, dimethyl formamide, acetonitrile, and a mixture of isopropyl alcohol and ethylacetate. Preferred solvents include isopropyl alcohol, a mixture of isopropyl alcohol and water, and ethanol. If desired, the product can be further purified by recrystallizing it one or more times from such a solvent. Alternatively a first solvent such as isopropyl alcohol can be used in a first crystallization followed by the use of a second solvent such as ethanol in at least one subsequent crystallization step. If desired, the mother liquor from such subsequent crystallization steps can be recycled and used as the solvent to dissolve the hippurate.

It has been found that the hippurate can retain solvent apparently in the crystal lattice. It has also been found that water appears to be preferentially retained compared to certain other solvents. Therefore to minimize any retention of other solvents by the salt, it is preferred that water be added to the solvent when compatible. For example, it is preferred that at least about 5 percent, more preferably 10 percent, and most preferably at least about 15 percent by volume water be used when isopropyl alcohol is used as the primary solvent. As is typical, it may be necessary to heat the solvent in order to maximize dissolution of the salt. By crystallization the salt can be thus prepared in purity exceeding 99%. Other salt forms which are not crystalline are not so readily purified and frequently require the employment of expensive, tedious chromatographic techniques for their purification.

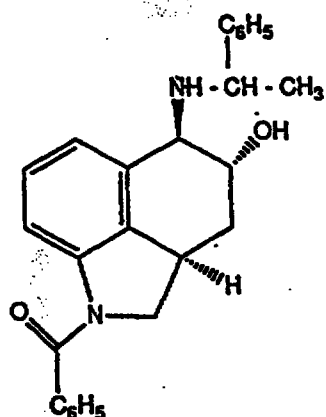
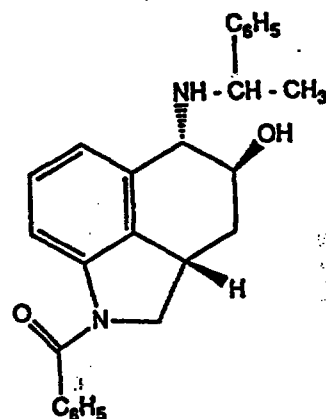
Organic and pharmaceutical chemists will recognize that the hippurate of the compound of Formula I contains one chiral center. The compound of this invention is useful whether it exists substantially as the R enantiomer, substantially as the S enantiomer, or as a mixture of the two enantiomers. The preferred embodiment is the hippurate of the compound of Formula I which is a substantially pure enantiomer, especially the R enantiomer.

If it is desired to prepare the racemic mixture of 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate, then the base compound can be prepared by the method disclosed by Flaugh, *supra*. However, the following method can be used to prepare a single enantiomer of the base compound, which may then be used to prepare a single enantiomer of the hippurate salt.

The following pair of enantiomers of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole can be selectively prepared by the methods of Leanna, *et al.*, *Tet. Lett.*, 30, no. 30, pp. 3935-3938 (1989).

III_aIII_b

The reaction of the racemic mixture of III_a and III_b with a primary amine containing a chiral center such as S-1-phenylethylamine produces a pair of diastereomers of the formulae:

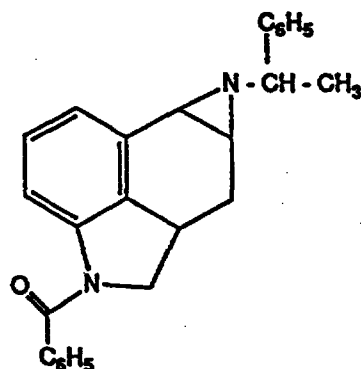
IV_aIV_b

The diastereomers can be separated by a number of methods frequently used in the art such as chromatography and selective crystallization.

A particularly advantageous method of preparing a substantially pure diastereomer of Formula IV_a in a single step is as follows. The reaction is conducted in *n*-butanol at a concentration of about 1 gram of the epoxide per 9 milliliters of solvent at about 90°C for about 16 hours. Upon being cooled to about room temperature, the diastereomer of Formula IV_b remains in solution, while the diastereomer of Formula IV_a crystallizes and can be collected by filtration.

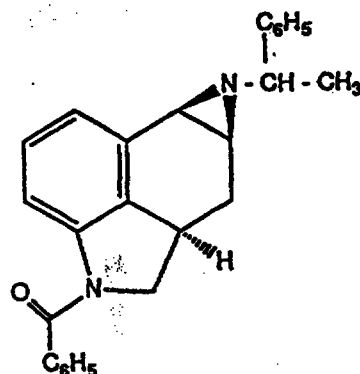
For simplicity of discussion, the subsequent intermediates and products shown below are those that result from the compound of Formula IV_a. Of course, the use of *R*-1-phenylethylamine instead of *S*-1-phenylethylamine in the above reaction will result in the selective crystallization of the compound which is the mirror image of Formula IV_a, and the use thereof in this synthesis results in subsequent intermediates and products which are the enantiomers of those shown below. Also other optically active primary amines in addition to 1-phenylethyl amine could be used.

The next step in the preparation of the preferred starting material for the compounds of the invention is to form an aziridine of Formula V.



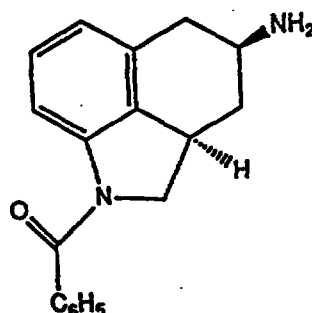
V

Several methods of forming aziridines from beta amino alcohols are known to the art. A preferred method is the reaction of the compound of Formula IV_a with triethylamine and methanesulfonyl chloride in dichloromethane. The following compound can be isolated from the reaction solution:



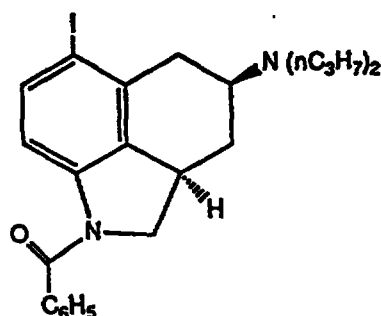
Va

15 The aziridine of Formula V is hydrogenolyzed over a noble metal catalyst such as palladium. It is important that the opening of the aziridine to form the secondary amine be substantially regiospecific, ie the aziridine should be opened to form substantially the 4-amino compound rather than the 5-amino compound. One such method is catalytic hydrogenolysis as taught by Y. Sugi and S. Mitsui, *Bull. Chem. Soc. Jap.*, 43, pp. 1489-1496 (1970). The preferred solvent is a mixture of acetic acid and methanol, and the reaction is
 20 conducted under approximately one atmosphere of hydrogen gas using a noble metal catalyst, preferably palladium. The reaction mixture is stirred at -5°C until the aziridine is consumed, as determined by thin layer chromatography or liquid chromatography. The product of this hydrogenolysis is a secondary amine, 1-benzoyl-4-(S-1-phenylethyl)amino-1,2,2a,3,4,5-hexahydrobenz[cd]indole, which need not be isolated. The hydrolysis is continued at about 55°C under about 1 atmosphere of hydrogen gas until the secondary
 25 amine is consumed, as determined by thin layer chromatography or liquid chromatography. Isolation, for example by crystallization, affords the substantially enantiomerically pure compound of Formula VI which is:



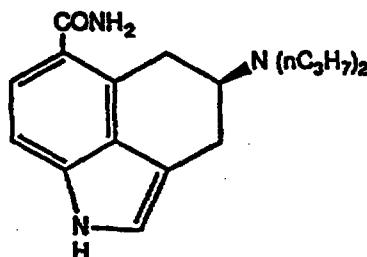
VI

40 The compound of Formula VII can be prepared from the compound of Formula VI by alkylation with propyl iodide in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, followed by iodination by iodine and orthoperiodic acid in the presence of an acid such as sulfuric acid or trifluoroacetic acid in a solvent such as aqueous acetic acid. Alternatively, iodination may precede
 45 alkylation.



VII

The following enantiomer of the compound of Formula I



Ia

can be prepared from the compound of Formula VII by reaction with an approximately equimolar mixture of carbon monoxide and ammonia in the presence of a catalyst, preferably a palladium catalyst such as bis-(triphenylphosphine)palladium chloride or bis(triphenylphosphine)palladiumbromide. The catalyst is preferably present in a ratio of about 0.05 mole per mole of reaction substrate. The preferred solvent is toluene, and the concentration of the reactant is about 0.5 to about 2.0 grams per 100 milliliters of solvent. The reaction vessel is sealed and the reaction mixture stirred at approximately 100 °C for approximately 6 hours. The use of such catalysts for the reaction of arylhalides with carbon monoxide is disclosed by Schoenberg and Heck, *Journal of Organic Chemistry*, 39, p. 3325 (1974) and Schoenberg, Bartoletti and Heck, *Journal of Organic Chemistry*, 39, p. 3318, (1974). The benzoyl group can then be removed by any of a number of methods known to the art, but preferably by reaction with approximately 4 equivalents of *n*-butyl lithium in freshly distilled tetrahydrofuran. The deprotection reaction is conducted at about -78°. The reaction is quenched by the addition of 1:1 (volume:volume) water and tetrahydrofuran, and the resulting 4-(di-*n*-propyl)amino-6-aminocarbonyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole is isolated by evaporation of the tetrahydrofuran, extraction from the aqueous phase into a solvent such as methylene chloride, and evaporation of the solvent. Oxidation of the hexahydrobenz-[cd]indole by reaction with manganese dioxide in acetic acid by the method disclosed by Flaugh in U.S. Patent No. 4,576,959 or palladium on carbon in methanol affords the desired 4-(di-*n*-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole.

The preparation of 4-(di-*n*-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate is accomplished by dissolving the base compound of Formula I in an inert solvent as discussed hereinabove and contacting it with about one or more equivalents of hippuric acid. The contacting can be conducted at a temperature of about 0 °C to about 100 °C, preferably from about 0 °C to about 25 °C. Suitable solvents include those discussed hereinabove.

The following examples are provided to illustrate the present invention and are not to be construed as limiting the scope thereof.

Example 1

Hippuric acid (0.60 grams, 3.3 millimoles) was combined with acetone (30 milliliters) and heated to 45 °C to dissolve the hippuric acid. (R)-4-(di-*N*-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole (1.0 g. 3.3 mmol) dissolved in acetone (10 ml) was added dropwise to the 45 °C solution of hippuric acid. The mixture was cooled with stirring under nitrogen. After 30 minutes at 25 °C, less than 1 milligram of seed crystals were added. Within one minute the solution was cloudy and crystals began to form and fall to the bottom of the flask. The mixture was stirred 30 minutes and then allowed to stand one hour. The mixture was filtered and the solid washed with reagent grade acetone. The solid was dried by air flow and then dried under vacuum to give 1.32 grams of white solid. Analysis of the solid gave the following results.

Melting point:	192-194 °C
UV (ethanol):	240nm ($\epsilon = 42,000$), 281nm ($\epsilon = 5650$)
IR (KBr):	3141, 3135, 1653, 1603, 1570, 1544, 1384, 1367, 1357, 1279, 1254
$[\alpha]_D$ =	-38.7° (methanol)
MS:	m/e = 300, 180

Analysis: (C ₂₇ H ₃₄ O ₄ N ₄)			
	C	H	N
Theory	67.76	7.16	11.71
Found	67.59	6.93	11.43

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X-Ray Crystallography provided unit cell dimensions in Å of: $a = 10.2974(5)$; $b = 12.0619(3)$; $c = 20.1382(6)$.
with $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$

10 volume = $2501.29 \pm 1.45 \text{ Å}^3$

Example 2

2.70 grams (15 mmoles) of hippuric acid were added to 40 ml of isopropyl alcohol. The mixture was
15 heated to 70°C to dissolve the hippuric acid. To the hot solution were added approximately 4.5 g (14.9 mmoles) of (S)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole dissolved in 25 ml of isopropyl alcohol. The solution was allowed to cool to room temperature, after 30 minutes white crystals formed. The mixture was stirred for 2 hours and then allowed to stand overnight. The mixture was filtered and the cake washed with isopropyl alcohol. The cake was dried at 40°C for 5 hours to yield 5.5 g of solid.
20 By NMR the solid contained about 3 weight percent isopropyl alcohol. The filtrate was concentrated to a foam, extracted with an aqueous base/methylene chloride mixture, and dried 24 hours at 50°C under vacuum. 5.4 g of the solid were dissolved in 65 ml of a mixture of isopropyl alcohol and water (90:10, v:v) at 85°C . The solution was allowed to cool to 25°C with stirring. The flask was scratched and seed crystals of the solid material which had been dissolved were added. The solution was placed in a refrigerator at 5°C ;
25 after one hour crystals had formed. Scratching the flask caused more crystal formation. The mixture was stored at 5°C overnight and filtered. The solid was washed with isopropyl alcohol and vacuum dried at 50°C for 24 hours to provide 3.78 g of white solid. Analysis of the white solid provided the following data:

Melting point: $190.5\text{--}192^\circ\text{C}$

IR (KBr): 3458, 3134, 2975, 1655, 1604, 1545, 1384, 1278 cm^{-1} .

30 $[\alpha]_D = +39.4^\circ$ ($c = 0.1$, methanol)

UV (ethanol): 278nm ($\epsilon = 4880$), 240nm ($\epsilon = 44000$)

Analysis (C ₂₇ H ₃₄ N ₄ O ₄)			
	C	H	N
Theory	67.76	7.16	11.71
Found	68.24	7.46	11.40

35

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Example 3

A racemic mixture of (RS)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate was prepared by combining equal amounts of the substantially pure enantiomeric indole hippurates.
45 150 mg of (R)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate were combined with 150 mg of the corresponding (S)-indole hippurate. The mixture was slurried in 10 ml of 0.2 normal HCl. 10 ml of ethyl acetate were added followed by 10 ml of 5 normal sodium hydroxide. The aqueous and organic layers were separated and the aqueous layer was extracted with 10 ml of ethyl acetate. The combined ethyl acetate layers were washed with 10 ml of 2 normal sodium hydroxide. The
50 liquid was dried with sodium sulfate and the ethyl acetate removed by vacuum to obtain 168 mg of white solid which is the racemic free base. 3 ml of isopropyl alcohol were added to the solid product and crystals formed. The crystals were dissolved by heating on a steam bath. This solution was added to a solution containing 100 mg (one equivalent) of hippuric acid in 1 ml isopropyl alcohol at 70°C . The solution was allowed to cool with stirring. A precipitate formed after 30 minutes. After 4 hours of stirring the mixture was
55 filtered and the solid washed with isopropyl alcohol. Vacuum drying gave 239 mg of white solid which had the following properties.

Melting Point: $175^\circ\text{--}177^\circ\text{C}$

$[\alpha]_D = 0.06^\circ$ (methanol)

The salt of the present invention is useful in treating disorders which can be benefited by a 5HT1A receptor agonist. Such disorders include anxiety, depression, senile dementia and consumptive disorders such as obesity, alcoholism and smoking.

The instant compound is usually administered in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art. Accordingly, the present invention also includes pharmaceutical compositions containing 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate associated with at least one pharmaceutically acceptable excipient.

In making the pharmaceutical compositions of the present invention, the hippurate salt is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid or liquid material which acts as a vehicle, carrier or medium for the active ingredient. Thus, the pharmaceutical compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, silicone oil, or mineral oil, wetting agents, emulsifying agents and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.01 mg to about 50 mg, more usually about 0.1 mg to about 25 mg, based on the free base, i.e., the free 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. It will be understood that the amount of the compound actually administered and the frequency of administration will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

In the following formulation examples, the term "Hippurate" is used to refer to the compound of the instant invention.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Hippurate	40.0
Starch Powder	220.0
Starch Flowable Powder (Pregelatinized Starch)	74.2
Silicone Fluid (350 centistokes)	0.8

The above ingredients are mixed and filled into hard gelatin capsules in 335 mg quantities.

Formulation 2

An alternative method to prepare hard gelatin capsules is provided as follows:

	Quantity (mg/capsule)
Hippurate	0.16
Starch	178.3
Starch Flowable Powder (Pregelatinized Starch)	51.0
Silicone Fluid (350 centistokes)	0.54

The starch is granulated with a solution of the hippurate in water. The granulation is dried overnight. This granulation is then passed through a 20 mesh sieve and mixed thoroughly with the starch flowable powder and silicone previously mixed and passed through a 10 mesh sieve. The formulation is then filled into hard gelatin capsules in 230 mg quantities.

Formulation 3

A tablet formulation is prepared using the ingredients below:

	Quantity (mg/tablet)
Hippurate	40.0
Cellulose, Microcrystalline	251.7
Colloidal Silicon Dioxide	4.5
Stearic Acid	2.3
Magnesium Stearate	1.5

The components are blended and compressed to form tablets each weighing 300 mgs.

Formulation 4

A tablet formulation is prepared using the components below:

	Quantity (mg/tablet)
Hippurate	0.16
Starch	104.84
Microcrystalline Cellulose	35.0
Polyvinylpyrrolidone (10% Solution in Water)	4.0
Sodium Carboxymethyl Starch	4.5
Magnesium Stearate	0.5
Talc	1.0

The starch and cellulose are passed through a 20 mesh sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a 4 mesh sieve. The granules are dried at 50-60 °C and passed through a 16 mesh sieve. The sodium carboxymethyl starch, magnesium stearate and talc that had previously been passed through a 30 mesh sieve, are then added to the granules and mixed. The mix is then compressed on a tablet machine to yield tablets each weighing 150 mg.

An alternate method of preparation is to pass the hippurate, starch and cellulose through a 20 mesh sieve and mix thoroughly. The solution of polyvinylpyrrolidone is then mixed with the resultant powders which are then passed through a 4 mesh sieve. The granules are dried at 50-60 °C and passed through a 16 mesh sieve. The sodium carboxymethyl starch, magnesium stearate and talc that had previously been passed through a 30 mesh sieve, are then added to the granules and mixed. The mix is then compressed on a tablet machine to yield tablets each weighing 150 mg.

**Claims**

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. 4-(Di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate.
2. The compound of Claim 1 which is substantially (4S)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate.
3. The compound of Claim 1 which is substantially (4R)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate.
4. A pharmaceutical formulation comprising the compound of Claims 1, 2 or 3 together with one or more pharmaceutically acceptable excipients, diluents, or carriers therefor.
5. A 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate as claimed in any of Claims 1, 2, or 3 for use as a pharmaceutical.
6. A 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate as claimed in any of Claims 1, 2 or 3 for use as an anxiolytic.
7. A 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate as claimed in any of Claims 1, 2 or 3 for treating depression in humans.
8. A method for preparing crystalline 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate as claimed in any one of Claims 1, 2 and 3 said method comprising (a) combining 4-(di-n-propyl)amino-1,3,4,5-tetrahydrobenz[cd]indole and hippuric acid and (b) crystallizing said hippurate from a solution to provide said crystalline hippurate.
9. The method of Claim 8 wherein said solution contains isopropyl alcohol in combination with at least about 10 volume percent water.
10. The method of Claim 8 wherein said crystalline hippurate is dissolved in a second solvent comprising isopropyl alcohol and at least about 15 volume percent water and 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate is then crystallized from said second solvent to provide recrystallized hippurate and mother liquor.
11. The method of Claim 10 wherein said mother liquor is recycled as said second solvent.
12. The method of Claim 8 wherein said crystalline hippurate is dissolved in a second solvent comprising ethanol and 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate is then recrystallized from said second solvent.

Claims for the following Contracting States : GR, ES

1. A process for preparing 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate which comprises contacting 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole with hippuric acid.
2. A process according to Claim 1 wherein (4R)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole is contacted with hippuric acid.
3. A process according to Claim 1 wherein (4S)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole is contacted with hippuric acid.
4. A process according to Claims 1, 2 or 3 wherein said hippurate is crystallized from a solution containing a suitable organic solvent and water.
5. The process of Claim 4 wherein said organic solvent is isopropanol or ethanol.



6. The process of Claim 4 wherein the crystalline hippurate is crystallized from a second solvent to provide recrystallized hippurate and a mother liquor.
7. A process for preparing a pharmaceutical formulation which comprises admixing a 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indole hippurate of Claims 1, 2 or 3 with one or more pharmaceutically acceptable excipients, carriers or diluents.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat.
2. Verbindung nach Anspruch 1, die im wesentlichen (4S)-4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat ist.
3. Verbindung nach Anspruch 1, die im wesentlichen (4R)-4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat ist.
4. Pharmazeutisches Präparat, umfassend die Verbindung der Ansprüche 1, 2 oder 3 zusammen mit einem oder mehreren pharmazeutisch annehmbaren Hilfsstoffen, Verdünnungsmitteln oder Trägern dafür.
5. 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat nach einem der Ansprüche 1, 2 oder 3 zur Verwendung als Pharmazeutikum.
6. 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat nach einem der Ansprüche 1, 2 oder 3 zur Verwendung als angstlösendes Mittel.
7. 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat nach einem der Ansprüche 1, 2 oder 3 zur Behandlung von Depressionen bei Menschen.
8. Verfahren zur Herstellung von kristallinem 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat nach einem der Ansprüche 1, 2 oder 3, wobei das Verfahren umfaßt, daß man (a) 4-(Di-n-propyl)-amino-1,3,4,5-tetrahydrobenz[cd]indol und Hippursäure vereinigt und (b) das Hippurat aus einer Lösung kristallisiert, was das kristalline Hippurat liefert.
9. Verfahren nach Anspruch 8, worin die Lösung Isopropylalkohol zusammen mit mindestens etwa 10 Volumen-% Wasser enthält.
10. Verfahren nach Anspruch 8, worin das kristalline Hippurat in einem zweiten Lösungsmittel gelöst wird, das Isopropylalkohol und mindestens etwa 15 Volumen-% Wasser umfaßt, und das 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat dann aus dem zweiten Lösungsmittel kristallisiert wird, um umkristallisiertes Hippurat und Mutterlauge zu liefern.
11. Verfahren nach Anspruch 10, worin die Mutterlauge als zweites Lösungsmittel zurückgeführt wird.
12. Verfahren nach Anspruch 8, worin das kristalline Hippurat in einem zweiten Lösungsmittel gelöst wird, das Ethanol umfaßt, und 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat dann aus dem zweiten Lösungsmittel umkristallisiert wird.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung von 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat, umfassend, daß man 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indol mit Hippursäure in Kontakt bringt.
2. Verfahren nach Anspruch 1, worin (4R)-4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indol mit Hippursäure in Kontakt gebracht wird.



3. Verfahren nach Anspruch 1, worin (4S)-4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz-[cd]indol mit Hippursäure in Kontakt gebracht wird.
4. Verfahren nach einem der Ansprüche 1, 2 oder 3, worin das Hippurat aus einer Lösung kristallisiert wird, die ein geeignetes organisches Lösungsmittel und Wasser enthält.
5. Verfahren nach Anspruch 4, worin das organische Lösungsmittel Isopropanol oder Ethanol ist.
6. Verfahren nach Anspruch 4, worin das kristalline Hippurat aus einem zweiten Lösungsmittel kristallisiert wird, um umkristallisiertes Hippurat und eine Mutterlauge zu liefern.
7. Verfahren zur Herstellung eines pharmazeutischen Präparats, umfassend, daß man ein 4-(Di-n-propyl)-amino-6-aminocarbonyl-1,3,4,5-tetrahydrobenz[cd]indolhippurat der Ansprüche 1, 2 oder 3 mit einem oder mehreren pharmazeutisch annehmbaren Hilfsstoffen, Trägern oder Verdünnungsmitteln vermischt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole.
2. Composé selon la revendication 1, qui est essentiellement l'hippurate de (4S)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole.
3. Composé selon la revendication 1, qui est essentiellement l'hippurate de (4R)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole.
4. Formulation pharmaceutique comprenant le composé des revendications 1, 2 ou 3, ensemble avec un ou plusieurs excipients, diluants ou supports pharmaceutiquement acceptables pour celui-ci.
5. Hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole selon l'une quelconque des revendications 1, 2 ou 3 pour l'utilisation comme produit pharmaceutique.
6. Hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole selon l'une quelconque des revendications 1, 2 ou 3 pour l'utilisation comme anxiolytique.
7. Hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole selon l'une quelconque des revendications 1, 2 ou 3 pour le traitement de la dépression chez l'homme.
8. Méthode pour la préparation de l'hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole cristallin selon l'une quelconque des revendications 1, 2 et 3, ladite méthode comprenant (a) la combinaison de 4-(di-n-propyl)amino-1,3,4,5-tétrahydrobenz[cd]indole et d'acide hippurique et (b) la cristallisation dudit hippurate à partir d'une solution de façon à fournir ledit hippurate cristallin.
9. Méthode selon la revendication 8, dans laquelle ladite solution contient l'alcool isopropylique en combinaison avec au moins environ 10 % volumiques d'eau.
10. Méthode selon la revendication 8, dans laquelle ledit hippurate cristallin est dissous dans un deuxième solvant comprenant de l'alcool isopropylique et au moins environ 15 % volumiques d'eau, et l'hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole est ensuite cristallisé à partir dudit deuxième solvant pour fournir de l'hippurate recristallisé et de la liqueur-mère.
11. Méthode selon la revendication 10, dans laquelle ladite liqueur-mère est recyclée en tant que ledit deuxième solvant.
12. Méthode selon la revendication 8, dans laquelle ledit hippurate cristallin est dissous dans un deuxième solvant comprenant de l'éthanol, et l'hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole est ensuite recristallisé à partir dudit deuxième solvant.



Revendications pour les Etats contractants suivants : GR, ES

1. Procédé pour la préparation de l'hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole, qui comprend la mise en contact du 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole avec l'acide hippurique.
2. Procédé selon la revendication 1, dans lequel le (4R)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole est mis en contact avec l'acide hippurique.
3. Procédé selon la revendication 1, dans lequel le (4S)-4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole est mis en contact avec l'acide hippurique.
4. Procédé selon les revendications 1, 2 ou 3, dans lequel ledit hippurate est cristallisé à partir d'une solution contenant un solvant organique approprié et de l'eau.
5. Procédé selon la revendication 4, dans lequel ledit solvant organique est l'isopropanol ou l'éthanol.
6. Procédé selon la revendication 4, dans lequel l'hippurate cristallin est cristallisé à partir d'un deuxième solvant de façon à fournir l'hippurate recristallisé et une liqueur-mère.
7. Procédé pour la préparation d'une formulation pharmaceutique qui comprend le mélange d'un hippurate de 4-(di-n-propyl)amino-6-aminocarbonyl-1,3,4,5-tétrahydrobenz[cd]indole selon les revendications 1, 2 ou 3 avec un ou plusieurs excipients, supports ou diluants pharmaceutiquement acceptables.