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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Novel Benzazepines and process for making same

We, SCHERICO LTD., of Topfarstrasse 5, Lucerne, Switzerland (formerly of Winkelriedstrasse 56, Lucerne, Switzerland), a body corporate constituted under the laws of Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivatives, to processes for preparing them, and pharmaceutical compositions in which they are present.

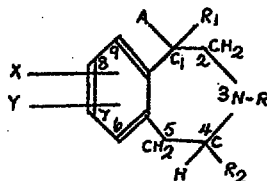
The novel compounds of this invention are 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivatives having hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl attached to the nitrogen atom at the 3-position, and optionally having an alkyl substituent at either or both of the 1- and 4-positions, but excluding 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine and 1 - phenyl - 7,8 - diethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, and the pharmaceutically acceptable acid addition and quaternary ammonium salts thereof.

The invention also includes pharmaceutical compositions which comprise, as an active ingredient, a 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivative having hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl

attached to the nitrogen atom at the 3-position, and optionally having an alkyl substituent at either or both of the 1- and 4-positions, or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof and, in association therewith, a pharmaceutically acceptable carrier compatible with the active ingredient.

The benzazepine compounds referred to in the form of the free base or acid addition and quaternary salts thereof exhibit anti-bacterial effects, central nervous system effects in that they exert anti-depressant and analgesic effects, and are also active in the cardiovascular system in that they exert a hypotensive effect, and, therefore, they are indicated as being useful therapeutic agents.

Preferred within the broad class of the novel 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine compounds of the invention are those of the general formula:



and the pharmaceutically acceptable acid addition salts and quaternary ammonium salts thereof, wherein each of X and Y individually represent hydrogen, hydroxy, alkyl, alkoxy or

halogen, or taken together, alkylenedioxy, A represents phenyl or substituted phenyl, R represents alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl, and each of R₁ and R₂ represents hydrogen or alkyl.

Advantageously, the hydrocarbon moiety in an alkyl, hydroxyalkyl, alkenyl or alkoxy, substituent contains no more than six carbon atoms, and in an alkylenedioxy substituent no more than three carbon atoms, and such substituents are referred to herein as lower alkyl, hydroxy-lower alkyl, lower alkenyl, lower alkoxy and lower alkylene dioxy substituents respectively. The terms "alkyl", alkoxy" and "alkenyl" as used herein and in the appended claims include cycloalkyl, cycloalkoxy and cycloalkenyl groups.

The lower alkyl substituents include such monovalent hydrocarbon radicals as methyl, ethyl, n-propyl, iso-propyl, butyl, n-butyl and iso-butyl (methyl is the preferred lower alkyl substituent); the hydroxy-lower alkyl substituents having 2-6 carbon atoms include hydroxypropyl, hydroxybutyl, but especially hydroxyethyl; the lower alkenyl substituents include straight and branched-chain monovalent hydrocarbon radicals having up to six carbon atoms and having one double bond, and include such radicals as allyl, butenyl, and pentenyl; lower alkoxy includes any such radical having up to six carbon atoms attached to the remaining portion of the benzazepine molecule through oxygen, and includes such radicals as methoxy, ethoxy, propoxy and butoxy; alkylene dioxy is preferably methylene dioxy, ethylene dioxy or propylene dioxy; and phenyl includes phenyl and substituted phenyl including halogeno (especially chloro), lower alkoxy (especially methoxy) and lower alkyl (especially methyl) substituted phenyl radicals, said substituents preferably being located in the para position, but they may also be located in the ortho and meta positions of the phenyl moiety.

The acid addition salts, which sometimes increase solubility and lend themselves better to formulation than do the free bases, include, for example, those prepared from hydrochloric, phosphoric, sulfuric, maleic, citric, salicylic, succinic and tartaric acids or their reactive derivatives. The quaternary ammonium salts include, for example, those prepared from such organic halides as methyl iodide, ethyl iodide, propyl chloride, benzyl chloride, and allyl bromide.

Among the compounds of Formula I within the invention and obtainable by a process according to the invention are: 1 - phenyl-3 - methyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 4 - methyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl-1,4 - dimethyl - 2,3,4,5 - tetrahydro - 1H,3 -

benzazepine, 1 - phenyl - 7 - chloro - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl-7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 3 - methyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl-3 - allyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 3β - hydroxyethyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine hydrobromide and 1 - phenyl - 3,3 - dimethyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepinium iodide.

The novel compounds of this invention and also 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine and 1 - phenyl - 7,8 - diethoxy-2,3,4,5 - tetrahydro - 1H,3 - benzazepine may be produced as racemic mixtures of their dextrorotary and levorotary isomers, whose separation may be effected by the usual well known techniques such as by the fractional crystallization of salts of optically active acids. Additionally, where position 4 is asymmetric, by proper choice of the optically active starting material, optically active products may be obtained directly.

The process provided by this invention for making the 1 - phenyl - 2,3,4,5 - tetrahydrobenzazepine derivatives involves, as an essential step, the intramolecular condensation of a compound which has the essential structural elements as well as the essential substituents, say a phenyl group attached to the carbon atom, which following upon the reaction will occupy the 1-position in the benzazepine nucleus of the desired product, but in which the azepine ring is broken at one point only, and which contains a reactive group attached to one or more of the atoms adjacent the break, whereupon the compound cyclises to form the azepine ring.

The expression "essential structural elements" as used herein, means that the compound contains the necessary number of carbon and nitrogen atoms properly disposed, for the formation, on cyclisation, of the benzazepine nucleus.

The expression "essential substituents" as used herein means those characteristic substituents of the desired product which, through necessity or choice, should be present in the compound prior to the formation of the benzazepine nucleus. The phenyl group attached to the carbon atom at the 1-position is an instance of an essential substituent.

The term "reactive group" as used herein means a group attached to an atom adjacent the break in the azepine ring which, either of itself or, when promoted by an =O substituent attached to an adjoining carbon atom, will react, if necessary in the presence of a catalyst or initiator for the reaction and under appropriate conditions of temperature and pressure, with a hydrogen atom or reactive group attached to a carbon atom also adjacent

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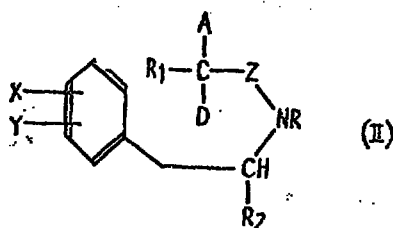
the break in the azepine ring, so as to cause a direct bond to be formed between the two atoms adjacent the break in the azepine ring which is thereby constituted.

Thus the compound which is subjected to intramolecular condensation may be a phenethylaminomethyl benzyl derivative having a reactive group attached to the terminal carbon atom, or it may be an ortho-benzyl-derivative of a phenethylamide compound containing a reactive group attached to the terminal carbon atom or the nitrogen atom or both, or it may be a phenethylcarbonyl benzyl derivative having a reactive group attached to the terminal carbon atom. When using the last-mentioned derivative the oxo-group in the 1 - phenyl - 2 - oxo 2,3,4,5 - tetrahydro-1H,3 - benzazepine derivative formed by the intramolecular condensation has to be reduced to methylene.

The 1H,3-benzazepine derivative resulting from the essential cyclisation may be subjected to one or more additional reaction steps as necessary or required to produce a desired 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine compound. Thus, for instance, it may be subjected to one or more of the following steps:

- (i) conversion, by any known reduction procedure, of an oxo group, say a 2-oxo group, into a methylene group;
- (ii) N-alkylation with the introduction of an alkyl, hydroxy-alkyl containing two or more carbon atoms, alkenyl or benzyl at the 3-position;
- (iii) introduction of one or more substituents into a benzene ring;
- (iv) transformation of the compound in the form of the free base into a pharmaceutically acceptable acid addition salt by reaction with a pharmaceutically acceptable acid or a reactive derivative thereof;
- (v) transformation of the compound in the form of the free base into a quaternary ammonium salt by reaction with a quaternizing agent.

A convenient process for making compounds of Formula (I) and compounds of this formula in which R is H involves, as the starting compound, a phenethylaminomethyl benzyl or phenethylcarbonyl benzyl derivative of the formula:



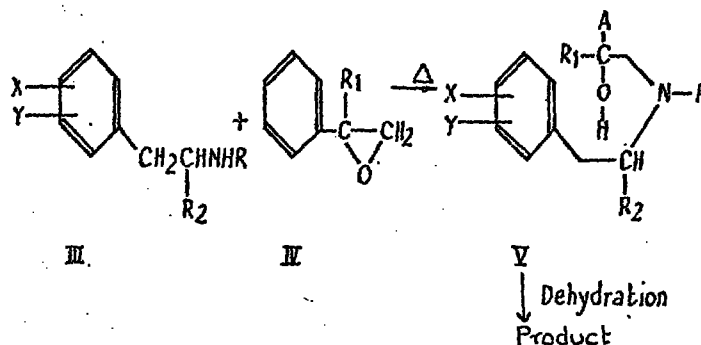
wherein X, Y, A, R, R₁ and R₂ have the same significance as for the compounds of Formula I, except that R may also be H, D is a reactive group and Z is a methylene group when a phenethylaminomethyl derivative is employed and an azo group when a phenethylcarbonyl derivative is employed. The compound II is subjected to intramolecular condensation, when the reactive group D reacts with a hydrogen atom attached to an adjacent carbon atom in the benzene ring, whereupon the compound cyclises so forming a carbon-carbon bond and constituting the azepine ring.

The cyclisation may be effected by one of a variety of methods. Thus, when as is often convenient, the reactive group D is a hydroxyl group, the phenethylaminomethyl benzyl alcohol or the phenethylcarbonyl benzyl alcohol compound is cyclized by dehydration using any known procedure, or by an intramolecular Friedel-Craft type reaction using catalysts such as aluminium chloride. The reactive group need not be hydroxy; it may, for instance, be halogen, particularly chlorine or bromine, or an -O-tosyl or an O-mesyl group or some other sulfonic acid ester, all of which undergo cyclisation reactions with or without catalysts such as aluminium chloride. Indeed, any reactive organic or inorganic ester group may be used.

The intermediary phenethylaminomethyl-benzyl alcohols are typically obtained by heating equimolar quantities of a styrene oxide with a phenethylamine compound. Preferably, the heating is effected on a steam bath, but the reaction may take place within the temperature range extending from just above room temperature to about 150° C. The carbinol intermediates so-obtained are then isolated by the usual techniques, such as by distillation and crystallization. In those instances, wherein it is desired to have a lower alkyl, say methyl, substituent at the 1-position of the benzazepine (i.e. when R₁ in Formula I represents methyl) then generally an α -methyl styrene oxide is employed. In those instances wherein it is desired to have a lower alkyl, say methyl, substituent in the 4-position of the benzazepine (e.g. when R₂ in Formula I represents methyl) then a branched-chain phenalkylamine, such as amphetamine may be employed. In those instances, wherein it is desired to have X and/or Y substituents in the benzenoid moiety of the benzazepine nucleus, the appropriately X,Y-substituted phenalkylamines may be employed. It will be understood that the 3-substituted benzazepines of Formula I may be directly formed by employing the appropriately N-substituted phenalkylamines, although in practice it is preferred not to employ such substituted phenalkylamines but rather, to N-alkylate a cyclic benzazepine of Formula I, wherein R represents hydrogen.

The foregoing phenethylaminomethyl benzyl alcohols are transformed into the desired benzazepines by means of an intramolecular cyclization, which may be effected by dehydrating the phenethylaminomethyl benzyl alcohol intermediates (V) using known procedures. These known procedures may involve treating the alcohol (V) with reagents such as polyphosphoric acid, sulfuric acid, zinc chloride and other similarly-acting dehydrating

agents. Preferably, the intermediate carbinols (V) are heated with polyphosphoric acid within a temperature range of about 80° C to 160° C whereby dehydration with concomitant cyclization occurs, although when using concentrated sulfuric acid it is preferred to effect dehydration at about -5° C to 20° C. The foregoing reactions are depicted schematically hereunder:

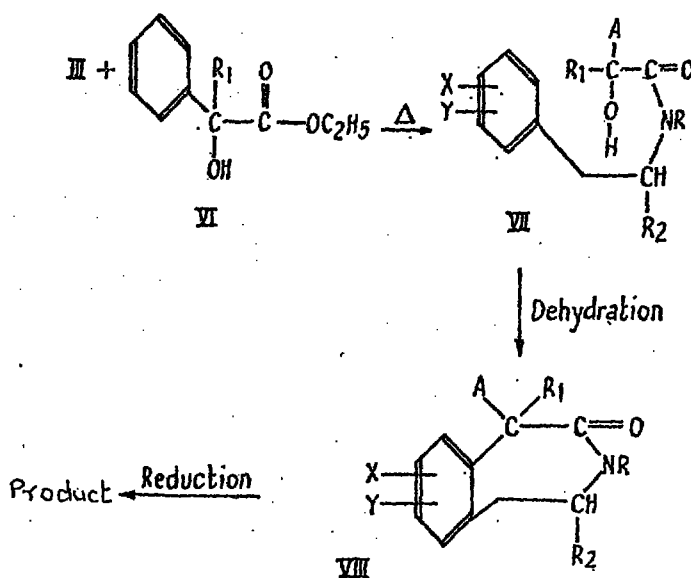


wherein X, Y, A, R, R₁ and R₂ have the same significance as for Formula (I), except that R may also be H.

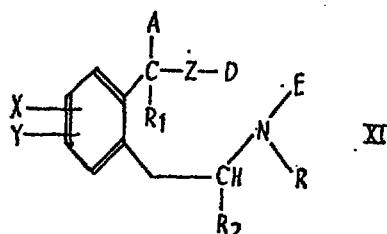
The 1-phenyl-2,3,4,5-tetrahydrobenzazepines may also be prepared from 1-phenyl-2-oxo-2,3,4,5-tetrahydrobenzazepine intermediates which may be prepared by condensing together the appropriate phenalkylamine (III) with an ester of mandelic acid (VI), for example, ethyl mandelate, to obtain the appropriate carbamyl alcohol (VII). Preferably, the condensation is effected by heating the starting compounds together on an oil bath at about 150°—190° for 2—6 hours, although temperatures within the range

of about 150°—200° C may be employed. The carbamyl alcohols (VII) are then dehydrated, preferably by reaction with an acid dehydrating agent, such as those previously described for the dehydration of the carbinol (V), so as to effect an intramolecular cyclization to form 2-oxo-benzazepine intermediates (VIII).

To obtain the 1H,3-benzazepine compound (I), the 2-oxo-benzazepine intermediate must be reduced. Any generally known reduction procedure, such as by reaction with lithium aluminium hydride in dioxane, may be employed. These reactions are depicted schematically hereunder:



Another convenient process for making the preferred compounds of formula I and similar compounds in which R is H involves, as the starting compound, a phenethylamino derivative of the formula:

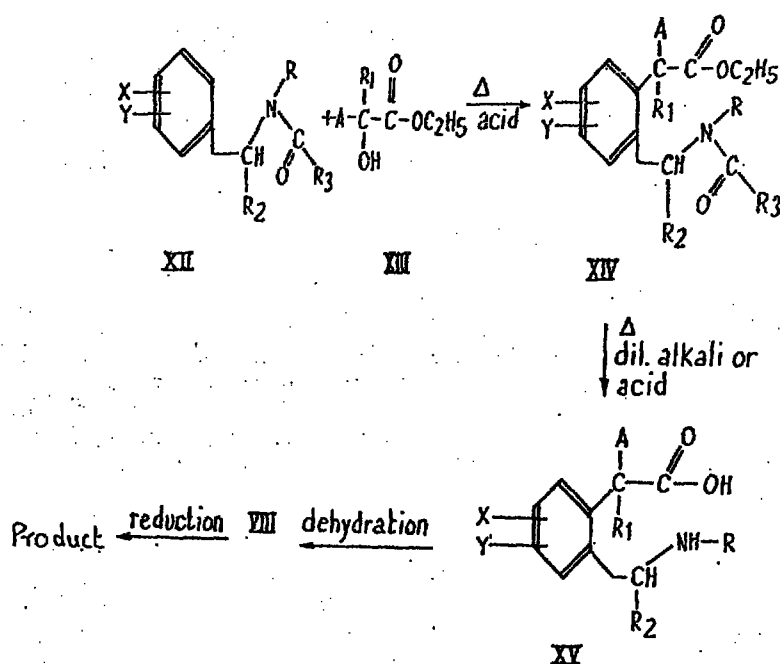


wherein X, Y, A, D, Z, R, R₁ and R₂ have the same significance as before, except that R may also be H and E represents hydrogen or a reactive group.

The compound XI is subjected to intramolecular condensation, when the reactive group D reacts with the hydrogen atom or the reactive group attached to the nitrogen atom, whereupon the compound cyclizes so forming a carbon-nitrogen bond and constituting the azepine ring. Typically, the reactive group D in the starting compound is a hydroxy, alkoxy, aryloxy or an aralkoxy group or some other group capable of forming a carbonium ion and E is hydrogen. Preferably, the starting compound of formula XI is one in which Z is oxo, D is hydroxy or alkoxy and E is hydrogen or acyl, i.e. a phenylacetic acid (or an ester thereof) derivative of a phenethylamino compound. In this event, the cyclization may be effected by dehydration using any known procedure.

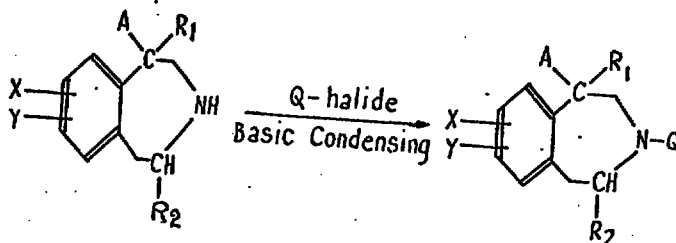
The starting compounds of formula XI

when in the form of a phenylacetic acid derivative of a phenethylamino compound may be obtained by condensing together, in the presence of an acid such as sulphuric or polyphosphoric acid, an N-phenethylcarbamyl derivative XII wherein R₃ represents an alkyl group, with an ester of a mandelic acid, for example, ethyl mandelate XIII, to obtain the ortho-(phenylacetic acid ethyl ester)-phenethylamino derivative XIV. Preferably, the condensation is effected on a steam bath, but the reaction may take place within the temperature range extending from just above room temperature to about 150° C. The compound XIV is then heated, for instance, on a steam bath, in the presence of acid or alkali, say dilute sodium bicarbonate, whereupon the ester group is hydrolyzed and there is fission between the nitrogen atom and the acyl group with elimination of the acyl group. The resulting compound XV, which is a phenylacetic acid derivative of a phenethylcarbamyl derivative, is then dehydrated, for instance, by reaction with an acid dehydrating agent or simply by heating *in vacuo*, so as to effect an intramolecular cyclization with the formation of a 2-oxo-benzazepine intermediate VIII. Under appropriate conditions, the compound XIV may be transformed directly, by intramolecular condensation, into the 2-oxo-benzazepine intermediate VIII. To obtain the desired 1H-3-benzazepine derivative I, the 2-oxo-benzazepine intermediate must be reduced. Any generally known reduction procedure, such as by reaction with lithium aluminium hydride in dioxane, may be employed. These reactions are depicted schematically hereunder:



In those instances, wherein the 1H,3-benzazepines have hydrogen in the 3-position thereof (i.e.—when R in Formula I represents

hydrogen) such benzazepines may be N-alkylated according to the following reaction scheme: 5



wherein Q represents alkyl, hydroxyalkyl having two or more carbon atoms, alkenyl (advantageously the hydrocarbon moiety is lower in each case), or benzyl, and X, Y, R₁, R₂ and A are as defined above. The foregoing reaction constitutes the condensation of an organic halide (preferably bromide or chloride) and typically it is effected in an inert solvent such as acetone, preferably at reflux temperature and in the presence of a basic condensing agent such as anhydrous potassium carbonate. Exemplary of such organic halides used are allyl bromide, benzyl bromide and methyl bromide.

The N-alkylation of those benzazepines which are formed through a 2-oxo-1H,3-benzazepine intermediate, may be effected before or after the necessary reduction of the 2-oxo group.

The 1H,3-benzazepine compounds obtained by either reaction schemes may, where desired, be transformed into a pharmaceutically acceptable acid addition or quaternary ammonium salt by an appropriate reaction.

The following examples illustrate the invention in both the product and process aspect.

EXAMPLE 1

This Example illustrates the preparation of 1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine by a process according to the invention.

A: N-[(β-hydroxy-β-phenyl)-ethyl]-2-phenyl-ethylamine:

Heat a well stirred mixture containing 82 g. of styrene oxide and 100 g. of phenethylamine on a steam bath for twelve hours. Distill (in vacuo) the resulting product to obtain the viscous product, which is recrystallized from petroleum ether.

B: 1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine:

To 100 ml. of concentrated sulfuric acid (which is kept at 0–5°C during this addition) add, in small portions, 15 g. of the N-[(β-hydroxy-β-phenyl)-ethyl]-2-phenylethylamine from Part A of this example and stir the resulting mixture for one hour. Pour the resulting mixture onto ice

and water, make strongly basic with sodium hydroxide, and extract the desired product with ether. Dry the ether extract over anhydrous potassium carbonate, filter and distill the desired product. The hygroscopic hydrochloride salt prepared with dry hydrogen chloride in ether is crystallized from isopropanol.

EXAMPLE 2

Following the procedure given in Part A of the preceding Example react together homoveratryl amine and styrene oxide to obtain the appropriate amino alcohol, N-[(β-hydroxy-β-phenyl)-ethyl]-2-(3',4'-dimethoxy)-phenyl-ethylamine (m.p. 95–98°C). This alcohol is then cyclized by the procedure given in Part B of the Example to yield 1-phenyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H,3-benzazepine (b.p. 198–200°C/2 mm.), which is converted to its acid maleate salt (m.p. 198–200°C), by reaction with maleic acid.

EXAMPLE 3

4-Methyl-1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine

A: N-[(β-Hydroxy-β-phenyl)-ethyl]-2-phenyl-isopropylamine:

Heat a well stirred mixture of 82 g. of styrene oxide and 100 g. of d-amphetamine on a steam bath for twelve hours. Distill (in vacuo) the resulting mixture to obtain a viscous product (b.p. 160–180°C/1mm.) which is crystallized from petroleum ether, m.p. 53–55°C, [α]_D²⁵ = +14.6°, (1% in ethanol).

B: 4-Methyl-1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine:

To 100 ml. of concentrated sulfuric acid (kept at 0°C) slowly and in small portions, add 15 g. of a finely ground powder of the optically active product of Part A. Stir for one additional hour after which time pour the mixture onto ice and water, make the resulting mixture strongly basic with sodium hydroxide, and extract with ether. Dry the ether extract over anhydrous potassium carbonate, filter and distill to obtain the desired product (b.p. 149–151°C/1 mm.). Its hygroscopic hydrochloride salt prepared with dry hydrogen chloride in ether is crystallized

from isopropanol chloride in ether is crystallized from isopropanol and melts at 206—207° C, $[\alpha]_D^{25} = -42.0^\circ$ (1% in dimethylformamide).

EXAMPLE 4

1-Methyl-1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine

A: α - Methyl - α - phenethylaminomethyl benzyl alcohol:

Heat a well stirred mixture containing 60 g. of α -methyl styrene oxide and 66 g. of phenethylamine on a steam bath for six hours and distill the resulting reaction mixture. The product (b.p. 160—168° C/1mm.), gives a hydrochloride salt which has a melting point of 142—145° C when recrystallized from acetonitrile.

B: 1 - Methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine:

Condense 28 gms. of α -methyl- α -phenethylaminomethyl benzyl alcohol in 250 ml. of concentrated sulfuric acid and extract the desired product with ether according to the procedure given in Part B of Example 3. Dry the ether extract over anhydrous potassium carbonate and distill the product at 150—160° C/1 mm. Recrystallize the product of this example from hexane (m.p. 76—79° C). The hydrochloride salt prepared with dry hydrogen chloride in ether melts at 228—229° C.

From the teachings of the foregoing Examples it will be clear that by employing the appropriately substituted reactants, a host of other benzazepines may be similarly prepared. Thus, by changing the reactants and by following substantially the same procedures outlined in Examples 1—4 there may, for instance, be prepared 1-phenyl-1,4-dimethyl-2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1,4 - dimethyl - 7 - chloro-2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1,4,7 - trimethyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 4 - methyl - 8 - hydroxy - 2,3,4,5 - tetrahydro-1H,3 - benzazepine, 1 - phenyl - 1,4 - dimethyl - 8 - methoxy - 2,3,4,5 - tetrahydro-1H,3 - benzazepine, 1 - phenyl - 7,8 - methylenedioxy - 2,3,4,5 - tetrahydro - 1H,3-benzazepine. The necessary phenethylamine starting materials for the preparation of the foregoing benzazepines are known *per-se* or may be prepared by methods obvious to one of ordinary skill in the art.

EXAMPLE 5

This Example illustrates the preparation of a benzazepine compound according to the invention using a phenethylcarbamiyl benzyl alcohol intermediate, and the preparation of the intermediate.

1-Phenyl-7-methoxy-2,3,4,5-tetrahydro-1H,3-benzazepine

A: N - (β - p - methoxy - phenethyl)-mandelamide:

Heat a well stirred solution of 25 g. of β -p-methoxyphenylethyl amine and 30 g. of ethyl mandelate in an oil bath at 180—190° C for three hours. Cool the reaction mixture and crystallize the desired product from ether (m.p. 75—76° C).

B: 1 - Phenyl - 2 - oxo - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine:

To 700 g. of polyphosphoric acid, slowly, and in small portions, add 20 g. of a finely ground powder of N - (β - p - methoxy-phenethyl) - mandelamide and slowly warm the resulting mixture to 100° C. Continue heating the mixture at 100° C for one hour. Allow the mixture to come to room temperature, pour the cooled mixture onto ice and water and extract with chloroform. Evaporate off (*in vacuo*) the chloroform solvent and recrystallize 1 - phenyl - 2 - oxo - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine from ethyl acetate (m.p. 169—171° C).

C: 1 - Phenyl - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine:

To a well stirred and refluxing suspension of 5 g. of lithium aluminium hydride in 200 ml. of dioxane, add in a dropwise fashion a solution of 10 g. of 1 - phenyl - 2 - oxo - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine in 250 ml. of dioxane and heat the resulting mixture at reflux for 3 hours. Cool the resulting mixture, and while maintaining the mixture at 20° C, (in a dropwise fashion) add 0.5 ml. (4 times) of water, 0.5 ml. (4 times) of 15% sodium hydroxide and 13.5 ml. of water and stir the reaction mixture for one hour. Filter off the precipitate of the inorganic material and distill the resulting filtrate to remove the solvents. Combine the residue with 100 ml. of 5% hydrochloric acid and 200 ml. of ether, stir the mixture until the residue dissolves, separate the aqueous extract, basify the aqueous extract with sodium hydroxide and extract with ether. Dry the ether extract with anhydrous potassium carbonate. Evaporate off the solvent and convert the desired product of this Example to its acid maleate salt by adding the product to maleic acid in ethyl acetate to yield 1 - phenyl - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine maleate (m.p. 196—197° C).

EXAMPLE 6

1-Phenyl-3-allyl-2,3,4,5-tetrahydro-1H,3-benzazepine

With vigorous stirring heat at reflux temperature a mixture containing 6 g. of 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 2.4 g. of allylbromide, 25 g. of anhydrous potassium carbonate and 250 ml.

- of anhydrous acetone for fourteen hours. Cool the resulting mixture, filter and distill off the acetone solvent. Dissolve the residue with ether and water, separate the water layer, dry and filter the ether layer and evaporate the ether solvent. Recrystallize the desired product from hexane (m.p. 65—68° C.). Prepare
- 5 1 - phenyl - 3 - allyl - 2,3,4,5 - tetrahydro-1H,3 - benzazepine hydrochloride (m.p. 203—205° C), by treating the product of this example with dry hydrogen chloride in ether.
- 10 By replacing the 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine of the foregoing Example with, for example, 1 - phenyl - 4 - methyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1,4 - dimethyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1,4 - dimethyl - 7 - chloro - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1,4,7 - trimethyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 4 - methyl - 8 - ethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1,4 - dimethyl - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 1 - methyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 1 - phenyl - 8 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine or 1 - phenyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine (as instances of particular benzazepine compounds) according to the procedure given in the Example to produce the corresponding N-methyl, N-ethyl, N-propyl, N-butyl, N-methylallyl, N-vinylethyl and N-benzyl substituted benzazepines.
- 15 70
- 20 75
- 25 80
- 30 85
- 35 90
- 40 95
- 45 100
- 50 105
- 55 110
- 60 115
- 65 120
- 125
- EXAMPLE 7
- 1-Phenyl-3,β-hydroxyethyl-2,3,4,5-tetrahydro-1H,3-benzazepine
- To a solution of 6 gm. of 1-phenyl-2,3,4,5-tetrahydro - 1H,3 - benzazepine in 50 ml. of ethanol, add 1 g. of ethylene oxide and keep the stoppered reaction mixture at room temperature for several days. Distill the resulting mixture and crystallize the oil residue from isopropylether (m.p. 95—97° C).
- EXAMPLE 8
- 1-phenyl-3-methyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H,3-benzazepine and 1-Phenyl-3,3-dimethyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H,3-benzazepinium iodide
- Heat, at reflux temperature a mixture containing 9 g. of 7,8 - dimethoxy - 1 - phenyl-2,3,4,5 - tetrahydro - 1H,3 - benzazepine, 15 ml. of 37% formaldehyde and 23 ml. of 90% formic acid for 18 hours. Add a solution of 5 ml. of concentrated hydrochloric acid in 10 ml. of water and evaporate the solution to dryness *in vacuo* on the steam bath. Add a 25 ml. portion of water to the residue and evaporate to dryness. Treat the residue with ether and excess sodium hydroxide solution, separate the ether solution, and dry, filter and evaporate the other solution. Crystallize 7,8 - dimethoxy - 3 - methyl - 1 - phenyl-2,3,4,5 - tetrahydro - 1H,3 - benzazepine residue from hexane, (m.p. 82—84° C). To 5 gms. of 7,8 - dimethoxy - 3 - methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine in 5 ml. of ethanol, add 5 ml. of methyl iodide and allow the resulting mixture to stand at room temperature for 15 hours, whereupon the desired 7,8 - dimethoxy - 3,3 - dimethyl - 1 - phenyl - 2,3,4,5 - tetrahydro-1H,3 - benzazepinium iodide crystallizes from the mixture (m.p. 246—249° C).

EXAMPLE 9

1-Phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H,3-benzazepine hydrobromide

- Heat, at reflux temperature, under a nitrogen atmosphere, a mixture containing 15 gm. of 1 - phenyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine and 110 ml. of 48% hydrobromic acid for 2.5 hours. On cooling the hydrobromide salt of the desired compound crystallizes. Filter and wash the crystals with alcohol to yield 1 - phenyl - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine hydrobromide (m.p. 283—285° C).

EXAMPLE 10

- This example illustrates the preparation of a benzazepine compound according to the invention using a phenylacetic acid derivative of a phenethylamino compound as an intermediate, and the preparation of the intermediate.

1-Phenyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H,3-benzazepine

- A: N - (3,4 - dimethoxy - 6 - phenylacetic acid-ethyl ester-phenethyl)-acetamide

- Warm 750 gm. of polyphosphoric acid to a temperature of 60—70° C and while continuously stirring the acid, add 18.1 gms. of N - (3,4 - dimethoxy - phenethyl)-acetamide. Heat the mixture on a steam bath until it is homogeneous, usually for ten to fifteen minutes. Add 18 gms. of ethyl mandelate dropwise over a period of five to ten minutes, and continue heating at 90—95° C on the steam bath for one hour. The resulting mixture is poured onto 2.5 kg. of ice and water and the crude product which is the desired acetamide is extracted with chloroform.

- B: 1 - Phenyl - 7,8 - dimethoxy - 2 - oxo - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine

- The extracts derived following the procedure of part A of this example are combined then washed with water and dilute sodium bicarbonate. The solvent is then removed on a steam bath and the residue heated *in vacuo* on the steam bath to constant weight. The product, which is 1 - phenyl - 7,8 - dimethoxy - 2 - oxo - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, is then crystallized from ethanol.

- C: 1 - Phenyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine

- 3 gms. of the compound derived from part B of this Example are added to a suspension of 1 g. of lithium aluminium hydride in 500 ml. of dioxane and refluxed with stirring for ten hours. The cooled solution is treated consecutively and dropwise with 2.7 ml. of water, 2.7 ml. of 15% sodium hydroxide and 8.1 ml. of water and is stirred for one hour at room temperature. The precipitate of in-

organic salts is filtered, washed with dioxane, and the combined filtrate and washings are concentrated *in vacuo* on the steam bath. The residue is taken up in ether, extracted with 50 ml. of 5% hydrochloric acid and the acid extract is basified with sodium hydroxide. The oil is extracted with ether, dried with anhydrous potassium carbonate, filtered, and the solvent is evaporated. The crude 1-phenyl-7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3-benzazepine is purified as its acid maleate salt.

EXAMPLE 11

This example illustrates the resolution of a racemic mixture of 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

42 gms. of 1 - phenyl - 2,3,4,5 - tetrahydro-1H,3 - benzazepine and 37 gms of (+) phenylsuccinic acid are dissolved in 90 per cent ethyl alcohol by warming them together. The solution is maintained at room temperature for several days without disturbing it. The resulting crystals are recovered by filtration, then washed with a small amount of cold alcohol prior to being recrystallized from 150 ml. of 90 per cent ethyl alcohol. The crystals are obtained in a yield of 15 gms., and they melt at 180—182° C with $[\alpha]_D^{25} = +55.2^\circ$ (1% in dimethylformamide). The free base is recovered from the salt with aqueous sodium hydroxide and ether following standard procedures and is then recrystallized from hexane. It melts at 78—80° C with $[\alpha]_D^{25} = -29.9^\circ$ (1% in dimethylformamide). The alcohol mother liquors from the washing and the recrystallization are combined, then concentrated *in vacuo* and the free 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine is recovered following standard procedures and using aqueous sodium hydroxide and ether. This partially resolved compound is further resolved using (–) phenylsuccinic acid in the above procedure to yield the optical isomer with the same melting point and an equal but opposite rotation.

The 1 - phenyl - 2,3,4,5-tetrahydro-1H,3-benzazepine derivatives of this invention, may be administered in the form of pharmaceutical compositions containing one or more of these compounds in association with a pharmaceutically acceptable carrier compatible therewith, and the compositions are included within the scope of this invention.

Such compositions may also contain other active compounds with which they are compatible including, for example, analgesics, antidepressants, antibiotics and proteolytic enzymes, the nature of which will be determined by the condition being treated.

The compositions may be in solid form such, for example, as tablets, pills and capsules, or in liquid form for oral administration, such, for example, as syrups, elixirs, emulsions and sterile injectables, or in the form of a cream or lotion.

The pharmaceutical compositions may be

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made by utilizing procedures known generally for the preparation of pharmaceutical compositions, all of which involve the deliberate association of the 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivative with a pharmaceutically acceptable carrier compatible therewith. Suitable carriers include, for example, water, gelatin, lactose, a starch, magnesium stearate, talc, a vegetable oil, benzyl alcohol, a gum, a polyalkylene glycol, and petroleum jelly.

The following examples are given by way of illustrating a few of the pharmaceutical compositions according to this invention, and the process by which they may be obtained. In each, the active benzazepine compound is 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, but other compounds within this invention may be substituted therefor.

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EXAMPLE A

The composition of this example is in the form of enteric coated tablets:

Component	Amount (mg/core)
25 1-Phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine	100.0
Citric Acid	1.0
Lactose, USP	33.5
Dicalcium Phosphate	70.0
30 Nonionic Surfactant (*Pluronic F-68)	30.0
Sodium Lauryl Sulfate	15.0
Polyvinylpyrrolidone	15.0
Polyethylene Glycol (*Carbowax 1500)	4.5
35 Polyethylene Glycol (Carbowax 6000)	45.0
Denatured Alcohol 50 ml/1000 cores	
40 Corn Starch	30.0
Dry	
Sodium Lauryl Sulfate	3.0
Magnesium Stearate	3.0
Tablet Weight	350.0

45 [*Pluronic and Carbowax are Registered Trade Marks]

Procedure:

The 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine is mixed with the citric acid, lactose, dicalcium phosphate, the pluronic and sodium lauryl sulfate. The above mixture is screened through a No. 60 screen and damp granulated with an alcoholic solution consisting of polyvinylpyrrolidone, carbowax 1500 and 6000. Add additional alcohol, if necessary, to bring powders to a pasty mass. Add corn starch and continue mixing until

uniform granules are formed. Pass through a No. 10 screen, tray and dry in an oven at 100° C for 12—14 hours. Reduce dried granulation through a No. 16 screen, add sodium lauryl sulfate and magnesium stearate, mix and compress into desired shape on a tablet machine.

Coating:

The above cores are treated with a lacquer and dusted with talc to prevent moisture adsorption. Sub-coat layers are added to round out the core. A sufficient number of lacquer coats are applied to make the core enteric. Additional sub-coats and smoothing coats are applied to completely round out and smooth the tablet. Color coats are applied until desired shade is obtained. After drying the coated tablets are polished to give the tablets an even gloss.

EXAMPLE B

The composition of this example is in the form of capsules:

Component	Amount (mg/capsule)	
1-Phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine	100.00	
Citric Acid	1.00	
Nonionic Surfactant (Pluronic, F-68)	40.00	85
Sodium Lauryl Sulfate	20.00	
Lactose	238.00	
Magnesium Stearate	1.00	
	400.0	90

Procedure:

Mix together 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, citric acid, pluronic, sodium lauryl sulfate and lactose. Pass through a No. 80 screen. Add magnesium stearate, mix and encapsulate into two-piece gelatin capsules of an appropriate size.

EXAMPLE C

The composition of this example is in the form of suppository.

Component	Amount (mg/2 gms)	
1-Phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine	100	
Theobroma Oil, Pharm. Grade to make	2 gms	105

Procedure:

Prepare a slurry of the 1-phenyl-2,3,4,5-tetrahydro - 1H,3 - benzazepine with a portion of the melted theobroma oil and pass the slurry through a suitable colloid mill until it is free of grittiness. Add sufficient melted

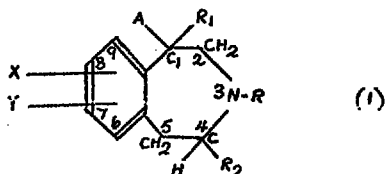
theobroma oil to bring the batch to final weight. Pour the melted mix, while maintaining uniformity, into appropriately prepared molds and allow to cool.

5 WHAT WE CLAIM IS:—

1. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives having hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl attached to the nitrogen atom at the 3-position, but excluding 1 - phenyl - 2,3,4,5 - tetrahydro-1H,3 - benzazepine and 1 - phenyl - 7,8 - diethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, and the pharmaceutically acceptable acid addition and quaternary ammonium salts thereof.

2. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in claim 1, which contain an alkyl substituent at either or both of the 1- and 4-positions.

3. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in claim 1, of the general formula:



and the pharmaceutically acceptable acid addition salts and quaternary ammonium salts thereof, wherein each of X and Y individually represent hydrogen, hydroxy, alkyl, alkoxy or halogen, or taken together, alkylene dioxy, A represents phenyl or substituted phenyl, R represents alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl, and each of R₁ and R₂ represents hydrogen or alkyl.

4. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in any one of claims 1 to 3, wherein any alkyl, hydroxyalkyl, alkenyl or alkoxy substituent if present contains no more than 6 carbon atoms, and an alkylene dioxy substituent if present contains no more than 3 carbon atoms.

5. 1 - Phenyl - 3 - methyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

6. 1 - Methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

7. 1 - Phenyl - 3 - methyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

8. 1 - Phenyl - 3β - hydroxyethyl-2,3,4,5-tetrahydro-1H,3-benzazepine.

9. 1 - Phenyl - 3 - allyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

10. 1 - Phenyl - 3 - ethyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

11. 1 - Phenyl - 1,4 - dimethyl - 2,3,4,5-tetrahydro - 1H,3 - benzazepine.

12. 1 - Phenyl - 7 - chloro - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

13. 1 - Phenyl - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

14. 1 - Phenyl - 7,8 - dihydroxy - 2,3,4,5-tetrahydro-1H,3-benzazepine hydrobromide.

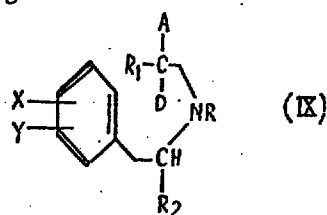
15. 1 - Phenyl - 3,3 - dimethyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepinium iodide.

16. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in claim 1 substantially as herein described.

17. Process for the preparation of a 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivative having hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl attached to the nitrogen atom at the 3-position, and independently having hydrogen or an alkyl substituent at the 1- and 4-positions which comprises subjecting a compound having the essential structural elements of the desired benzazepine product, but in which the azepine ring is broken at one point only, said compound containing a reactive group attached to one or more of the atoms adjacent the break, to intramolecular condensation whereupon the compound undergoes cyclization to form the azepine ring.

18. Process as claimed in claim 17, wherein the compound which is subjected to intramolecular condensation is a phenethylaminomethyl benzyl derivative having a reactive group attached to the terminal carbon atom.

19. Process as claimed in claim 18, wherein the phenethylaminomethyl benzyl derivative has the general formula:



wherein X and Y individually represent hydrogen, hydroxy, alkyl, alkoxy or halogen, or taken together, alkylene dioxy, A represents phenyl or substituted phenyl, D is a reactive group, R represents hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl, and each of R₁ and R₂ represents hydrogen or alkyl.

20. Process as claimed in claim 17, wherein the compound which is subjected to intramolecular condensation is a phenethylcarbamyl benzyl derivative having a reactive group attached to the terminal carbon atom, and the oxo-group in the 1 - phenyl - 2 - oxo - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivative so-obtained is reduced to methyl-

21. Process as claimed in claim 20, wherein



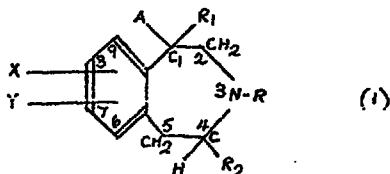
theobroma oil to bring the batch to final weight. Pour the melted mix, while maintaining uniformity, into appropriately prepared molds and allow to cool.

5 WHAT WE CLAIM IS:—

1. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives having hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl attached to the nitrogen atom at the 3-position, but excluding 1 - phenyl - 2,3,4,5 - tetrahydro-1H,3 - benzazepine and 1 - phenyl - 7,8 - diethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine, and the pharmaceutically acceptable acid addition and quaternary ammonium salts thereof.

2. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in claim 1, which contain an alkyl substituent at either or both of the 1- and 4-positions.

3. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in claim 1, of the general formula:



25 and the pharmaceutically acceptable acid addition salts and quaternary ammonium salts thereof, wherein each of X and Y individually represent hydrogen, hydroxy, alkyl, alkoxy or halogen, or taken together, alkylene dioxy, A represents phenyl or substituted phenyl, R represents alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl, and each of R₁ and R₂ represents hydrogen or alkyl.

30 4. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in any one of claims 1 to 3, wherein any alkyl, hydroxyalkyl, alkenyl or alkoxy substituent if present contains no more than 6 carbon atoms, and an alkylene dioxy substituent if present contains no more than 3 carbon atoms.

5. 1 - Phenyl - 3 - methyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

45 6. 1 - Methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

7. 1 - Phenyl - 3 - methyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

8. 1 - Phenyl - 3β - hydroxyethyl-2,3,4,5-tetrahydro-1H,3-benzazepine.

9. 1 - Phenyl - 3 - allyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

10. 1 - Phenyl - 3 - ethyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

55 11. 1 - Phenyl - 1,4 - dimethyl - 2,3,4,5-tetrahydro - 1H,3 - benzazepine.

12. 1 - Phenyl - 7 - chloro - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

13. 1 - Phenyl - 7 - methoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine.

14. 1 - Phenyl - 7,8 - dihydroxy - 2,3,4,5-tetrahydro-1H,3-benzazepine hydrobromide.

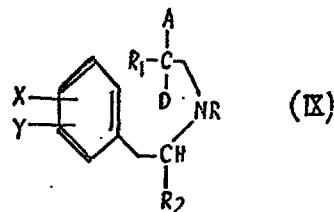
15. 1 - Phenyl - 3,3 - dimethyl - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H,3 - benzazepinium iodide.

16. 1 - Phenyl - 2,3,4,5 - tetrahydro-1H,3-benzazepine derivatives as claimed in claim 1 substantially as herein described.

17. Process for the preparation of a 1 - phenyl - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivative having hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl attached to the nitrogen atom at the 3-position, and independently having hydrogen or an alkyl substituent at the 1- and 4-positions which comprises subjecting a compound having the essential structural elements of the desired benzazepine product, but in which the azepine ring is broken at one point only, said compound containing a reactive group attached to one or more of the atoms adjacent the break, to intramolecular condensation whereupon the compound undergoes cyclization to form the azepine ring.

18. Process as claimed in claim 17, wherein the compound which is subjected to intramolecular condensation is a phenethylaminomethyl benzyl derivative having a reactive group attached to the terminal carbon atom.

19. Process as claimed in claim 18, wherein the phenethylaminomethyl benzyl derivative has the general formula:



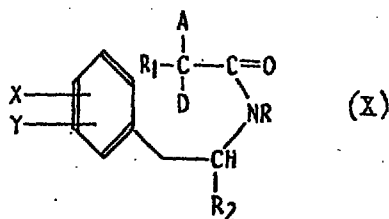
wherein X and Y individually represent hydrogen, hydroxy, alkyl, alkoxy or halogen, or taken together, alkylene dioxy, A represents phenyl or substituted phenyl, D is a reactive group, R represents hydrogen, alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl, and each of R₁ and R₂ represents hydrogen or alkyl.

20. Process as claimed in claim 17, wherein the compound which is subjected to intramolecular condensation is a phenethylcarbamiyl benzyl derivative having a reactive group attached to the terminal carbon atom, and the oxo-group in the 1 - phenyl - 2 - oxo - 2,3,4,5 - tetrahydro - 1H,3 - benzazepine derivative so-obtained is reduced to methylene.

21. Process as claimed in claim 20, wherein

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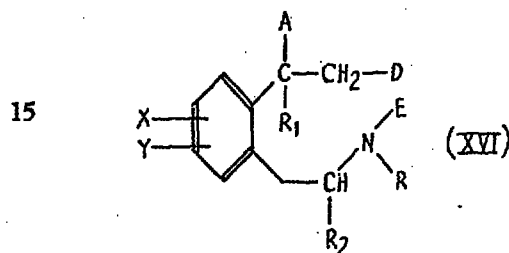
the phenethylcarbamyl benzyl derivative has the formula:



5 wherein X, Y, A, D, R, R₁ and R₂ have the same significance as in Claim 19.

22. Process as claimed in claim 17 wherein the compound which is subjected to intramolecular condensation is an ortho-benzyl-derivative of a phenethylamide compound containing a reactive group attached either to the terminal carbon atom or to the nitrogen atom or to both.

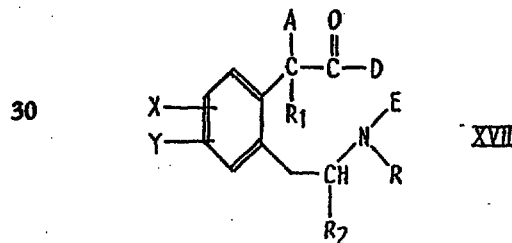
23. Process as claimed in claim 22, wherein the compound has the formula:



15 wherein X, Y, A, D, R, R₁ and R₂ have the same significance as in Claim 19 herein, and E represents hydrogen or a reactive group.

24. Process as claimed in claim 17, wherein the compound which is subjected to intramolecular condensation is an ortho-(phenyl-acetic acid)-phenethylamino compound in the form of the free acid or a functional derivative thereof, and the oxo-group in the 1-phenyl-2-oxo-2,3,4,5-tetrahydro-1H,3-benzazepine derivative so obtained is reduced to methylene.

25. Process as claimed in claim 24, wherein the compound has the formula:



30 in which X, Y, A, D, R, R₁ and R₂ have the same significance as in Claim 19 herein, and E represents hydrogen or a reactive group.

26. Process as claimed in claim 19, 21, 23 or 25, wherein an alkyl, hydroxyalkyl, alkenyl or alkoxy substituent contains no more than 6 carbon atoms, and an alkylene dioxy sub-

stituent contains no more than 3 carbon atoms.

27. Process as claimed in any one of claims 17 to 26, wherein the reactive group D in the starting compound is hydroxy, and the intramolecular condensation with concomitant cyclization involves dehydration of the starting compound.

28. Process as claimed in claim 27, wherein the dehydration is effected by heating the compound *in vacuo*.

29. Process as claimed in claim 27, wherein the dehydration is effected by treating the compound with an acid dehydrating agent.

30. Process as claimed in claim 29, wherein the dehydration is effected by treating the compound at a temperature of between 80° to 160° C with polyphosphoric acid.

31. Process as claimed in claim 29, wherein the dehydration is effected by treating the compound at a temperature of between -5° to 20° C with concentrated sulphuric acid.

32. Process as claimed in any one of claims 20-21, 24-25, and 26-31, wherein the reduction of the oxo-group in the 1-phenyl-2-oxo-2,3,4,5-tetrahydro-1H,3-benzazepine derivative is accomplished using lithium aluminium hydride in a solvent such as dioxan.

33. Process as claimed in any one of claims 17-32, wherein the 1-phenyl-1H,3-benzazepine derivative resulting from the intramolecular condensation is subjected to one or more of the following finishing procedures:

- (i) N-alkylation with the introduction of alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl at the 3-position;
- (ii) introduction of one or more substituents into a benzene ring;
- (iii) transformation of the compound in the form of the free base into a pharmaceutically acceptable acid addition salt;
- (iv) transformation of the compound in the form of the free base into a quaternary ammonium salt;
- (v) resolution of a racemic mixture into its optical isomers.

34. Process as claimed in claim 17 or 33, substantially as herein described with particular reference to any one of Examples 1 to 11.

35. 1-Phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine derivatives whenever obtained by a process as claimed in any one of claims 17-34.

36. Process as claimed in claim 27 when appendant to 18 or 19, wherein the phenethylaminomethyl benzyl alcohol compound is prepared by condensing together a styrene oxide compound with a phenethylamine compound.

37. Process as claimed in claim 36, wherein



the phenethylaminomethyl benzyl alcohol compound is prepared by condensing styrene oxide with phenethylamine, homoveratryl amine, d-amphetamine, or β -p-methoxyphenylethyl amine.

38. Process as claimed in claim 36, wherein the phenethylaminomethyl benzyl alcohol compound is prepared by condensing an α -alkyl, preferably an α -lower alkyl styrene oxide with phenethylamine, homoveratryl amine or d-amphetamine.

39. Process as claimed in any one of claims 36—38, wherein the starting compounds are condensed together in equimolar quantities.

40. Process as claimed in any one of claims 36—39, wherein the condensation is effected in the temperature range extending from just above ambient temperature to about 150° C.

41. Process as claimed in claim 27 when appendent to 20 or 21, wherein the phenethylcarbamyl benzyl alcohol compound is prepared by condensing together a mandelic acid ester with a phenethylamine compound.

42. Process as claimed in claim 41, wherein the phenethylcarbamyl benzyl alcohol is prepared by condensing ethyl mandelate with phenethylamine, homoveratryl amine, d-amphetamine or β -p-methoxyphenylethyl amine.

43. Process as claimed in claim 41 or 42, wherein the condensation is effected in the temperature range extending from 150°—200° C.

44. Process as claimed in claim 36 or 41, substantially as herein described.

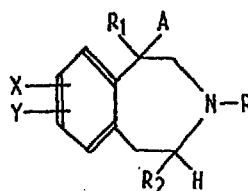
45. Process as claimed in claim 24, wherein the ortho-(phenylacetic acid) derivative of a phenethylamino compound is prepared by condensing together in the presence of an acid an N-phenethylcarbamyl derivative with an ester of mandelic acid and then treating the resulting ortho-(phenylacetic acid ester)-phenethylamino compound so as to eliminate the ester grouping and the acyl group attached to the nitrogen atom.

46. Process as claimed in claim 45, substantially as herein described.

47. A pharmaceutical composition which comprises, as an active ingredient, a 1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine derivative having hydrogen, alkyl, hydroxy-alkyl containing two or more carbon atoms,

alkenyl or benzyl attached to the nitrogen atom at the 3-position, and optionally having an alkyl substituent at either or both of the 1- and 4-positions, or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof and, in association therewith, a pharmaceutically acceptable carrier compatible with the active ingredient.

48. A pharmaceutical composition as claimed in claim 47, wherein the active ingredient is a 1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine compound of the general formula:



wherein each of X and Y individually represents hydrogen, hydroxy, alkyl, alkoxy or halogen, or taken together, alkylene dioxy, A represents phenyl or substituted phenyl, R represents alkyl, hydroxyalkyl containing two or more carbon atoms, alkenyl or benzyl and each of R₁ and R₂ represents hydrogen or alkyl, or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof.

49. A pharmaceutical composition as claimed in claim 47 or 48, substantially as herein described with particular reference to Examples A to C herein.

50. Process for making a pharmaceutical composition as claimed in claim 47 or 48, wherein the 1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine derivative is brought into a form suitable for therapeutic administration.

51. Process as claimed in claim 50, wherein the 1-phenyl-2,3,4,5-tetrahydro-1H,3-benzazepine derivative is admixed with a pharmaceutical carrier compatible therewith.

52. Process as claimed in claim 50 or 51, substantially as herein described.

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