United States Patent Office 3,225,031 Patented Dec. 21, 1965

3,225,031

PHENYL-BENZAZEPINES AND METHODS FOR THEIR MANUFACTURE

Margaret H. Sherlock, Bloomfield, N.J., assignor to Schering Corporation, Bloomfield, N.J., a corporation of New Jersey

No Drawing. Filed July 22, 1963, Ser. No. 296,431
11 Claims. (Cl. 260—239)

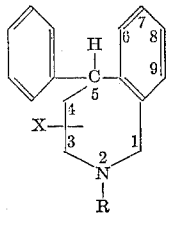
This invention relates to compositions of matter identifiable in the art of chemistry as 5-phenyl-tetrahydro-2-benzazepines and to processes for making and using such compositions.

The invention sought to be patented in its composition aspect is described as residing in the concept of a chemical compound having the molecular structure of 2,3,4,5-tetrahydro-1H-2-benzazepine having a phenyl substituent at the 5-position and at the 2-position having a member of the group consisting of hydrogen, lower alkyl and phenyl lower alkyl. Included within this concept are the acid addition salts and the quaternary salts thereof.

The invention sought to be patented in its process aspect is described as residing in the concept of that step which comprises heating at an elevated temperature a member of the group consisting of an o-R_1R_2-aminomethyldiphenylmethane and the acid addition salts thereof having a lower alkyl group of at least two carbon atoms attached to the methane carbon atom, the β-carbon atom of said alkyl group having a substituent of the group represented by R_1R_2 amino-, halogen (preferably chloro or bromo), tosyloxy and mesyloxy, wherein R_1 and R_2 represent methyl and benzyl, said heating at elevated temperature continued until substantial transformation into a tetrahydrobenzazepine compound is effected. Following the heating step, it may be necessary to de-alkylhalogenate depending upon the nature of the product formed.

The tangible embodiments of the invention in the form of the free base or acid addition salt thereof, possess the inherent applied use characteristics of exerting an effect upon the central nervous system manifest by a stimulant action as determined by pharmacological evaluation. They are thus useful in elevating mood, or establishing a wakefulness. At higher doses than that required to produce a stimulant effect, these compounds elicit an analgesic response. In the form of their nontoxic quaternary salts, the tangible embodiments are of value as anticholinergic or parasympathetic blocking agents.

The tangible embodiments of this invention are chemical compounds having the structural formula



I

wherein R is a member of the group consisting of H, lower alkyl and phenyl-lower alkyl, and X is a member

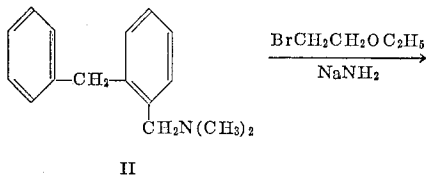
of the group consisting of H and methyl. Included within the foregoing are the acid addition salts and quaternary salts of the bases depicted therein. The system of numbering the nuclear atoms is set forth in the formula.

As stated heretofore, the tangible embodiments of this invention are prepared by heating an o-dimethylaminomethyldiphenylmethane or an o-dibenzylaminomethyldiphenylmethane or an o-N-benzyl-N-methylaminomethyldiphenylmethane, the methane carbon atom of which bears a lower alkyl group having at least two carbon atoms, the β-carbon atom of said alkyl group bearing a substituent such as dimethylamino, dibenzylamino, halogen (preferably chloro or bromo), tosyloxy and mesyloxy. Upon heating such a material at substantially elevated temperatures, ring closure occurs resulting in a compound of Formula I. Where the aforementioned substituent is an amino function as described heretofore, the cyclized product is a tertiary amine of Formula I. Where the substituent is halogen, the product formed is a quaternary salt which may be de-alkylhalogenated to form the tertiary amine.

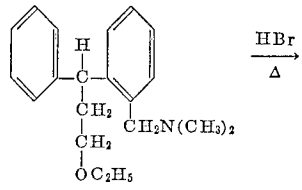
It will be apparent to one skilled in the art that precursors of the aforementioned starting materials, such as those possessing a hydroxy or lower alkoxy (preferably methoxy or ethoxy) group in the β-position of the aforementioned alkyl group, may be used by reacting said oxy compounds with a reagent which replaces the oxy function by halogen and then heating the halogenated product. For example, where the substituent is ethoxy, such a compound is heated with a hydrohalic acid, preferably hydrobromic acid, whereby the ethoxy group is replaced by bromo. Indeed, the o-R_1R_2-aminomethyl group simultaneously may form a hydrobromide salt. This intermediate, which is the starting material of the process aspect of my invention is preferably not isolated but is heated in situ in the presence of hydrobromic acid resulting in in situ ring closure forming a benzazepinium quaternary bromide. This method is outlined in further detail in subsequent passages. On the other hand, where the substituent is hydroxy, such a compound is reacted with thionyl chloride, for example, and heated in situ. The reaction with thionyl chloride effects replacement of the hydroxy by chloro with probable simultaneous formation of a hydrochloride of the o-R_1R_2-aminomethyl group. Upon heating in situ, ring closure occurs with the formation of a benzazepinium quaternary chloride. This reaction also is set forth in more detail in subsequent passages. It is thus apparent that such reactions whereby the starting materials of my invention in its process aspect are formed in situ and acted upon in situ are full equivalents of my invention in its process aspect.

A preferred method for preparing the tangible embodiment represented by Formula I, wherein R is methyl consists of alkylating o-dimethylaminomethyldiphenylmethane (II) with β-bromoethyl ethyl ether in the presence of a basic condensing agent such as sodamide in liquid ammonia. The β-ethoxyethyl analog (III) formed thereby is heated with a strong acid, preferably concentrated hydrobromic acid, whereby the benzazepinium bromide (IV) is formed. (As stated heretofore, the "bromo hydrobromide" formed by the action of hydrobromic acid is the starting material of my invention in its process aspect and is acted upon in situ by heating.) Heating the quater-

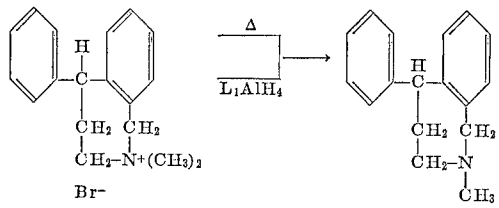
nary salt eliminates the element of methyl bromide resulting in the formation of tertiary amine (V). The quaternary salt may alternatively be de-methobrominated by reaction with lithium aluminum hydride or an alkali metal borohydride. This reaction sequence is depicted as follows:



II

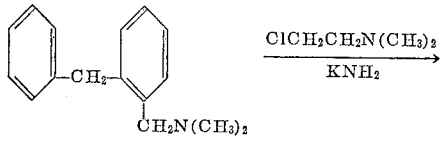


III

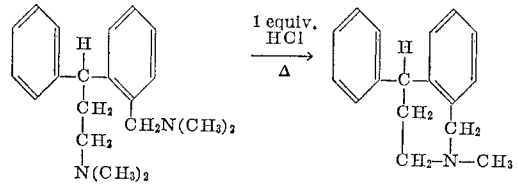


IV V

In place of the bromoethyl ether, there may be employed an alkylating agent such as dimethylaminoethyl chloride. The diamine, VI, thus formed is then transformed into its monohydrochloride salt and heated whereby cyclization occurs. The free base (VII) is obtained by rendering the cyclized residue alkaline and extracting with an organic solvent such as ether. This reaction sequence is shown as follows:



II

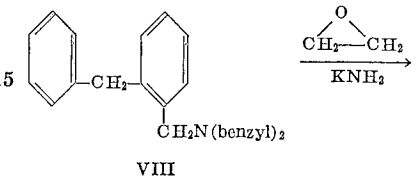


VI VII

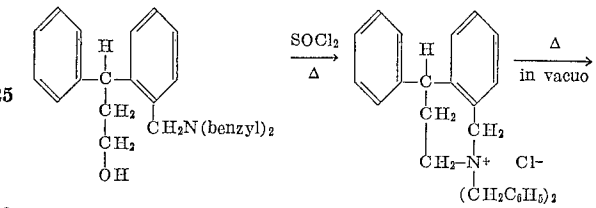
It is apparent that the dimethylaminoethyl chloride may carry an alkyl substituent such as methyl or ethyl

on either one of its carbon atoms, for example, 2-dimethylaminopropyl chloride. Two products are accordingly formed with this reagent: one having the alkyl substituent in the 2-position and the other in the 3-position.

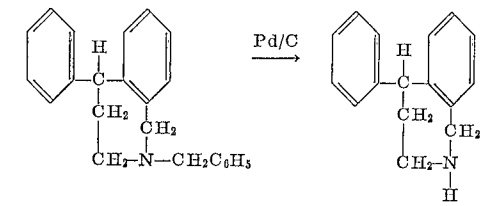
A further method for arriving at the compounds of Formula I wherein R is hydrogen is that depicted by the following reaction scheme:



VIII



IX X



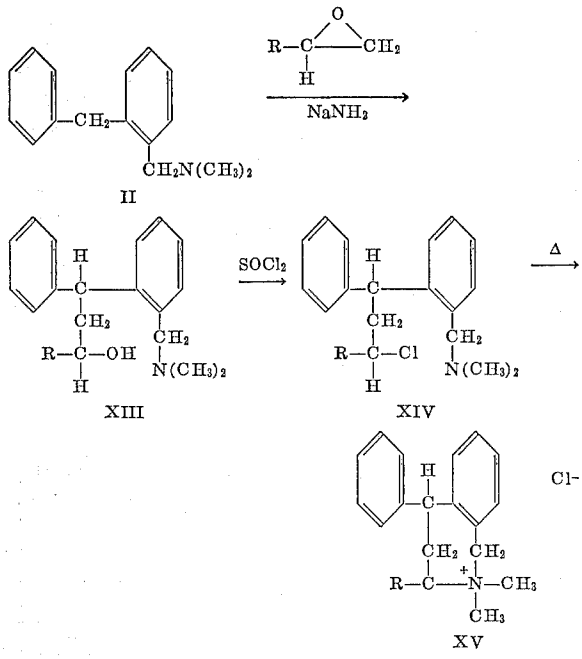
XI XII

In this sequence, o-dibenzylaminodiphenylmethane (VIII) is alkylated with ethylene oxide to produce the hydroxy intermediate (IX). Replacement of the hydroxy group by chlorine is effected by thionyl chloride and heating results in the formation of the quaternary benzyl chloride (X). (An intermediary "chlorohydrochloride" which is the starting material for the process aspect of my invention is formed and acted upon in situ.) Elimination of benzyl chloride yielding XI is accomplished by heating the dry quaternary salt in vacuo and debenzylation effected by reduction with hydrogen on a palladium charcoal catalyst. There is thus obtained the secondary amine XII. The nitrogen atom of XII may now be alkylated, if desired, by known means to yield the tertiary amine, i.e. R=lower alkyl or phenyl lower alkyl.

It will be apparent to one skilled in the art that by utilizing 1,2-propylene oxide in place of ethylene oxide analogous reactions take place with the methyl group appearing as a substituent on the heterocyclic ring, most probably in the 3-position. This accordingly is a means for preparing such an analogous product.

The quaternary ammonium salts are prepared in the known manner by reacting the tertiary amine of Formula I with a quaternizing agent such as a lower alkyl halide or sulfate. An alternative method is that wherein an o-dimethylaminomethyldiphenyl methane (II) is alkylated with an ethylene oxide as described heretofore and the hydroxy compound (XIII) treated with thionyl chloride.

The chloro compound (XIV) formed thereby upon heating is cyclized to yield the methyl quarternary salt (XV).



In the foregoing R represents H or methyl. It is necessary to treat the product of the reaction of XIII with thionyl chloride with alkali in order to prepare the free base XIV.

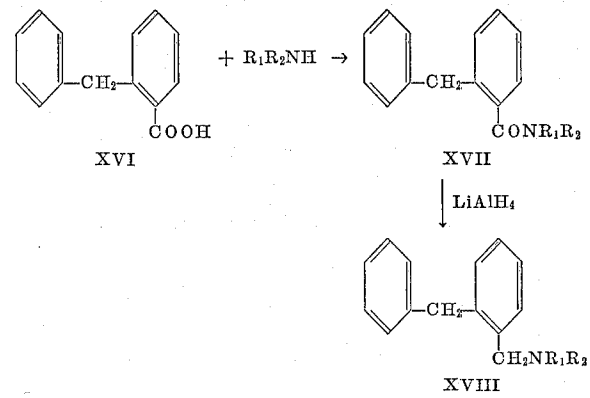
In the reaction schemes illustrated heretofore, the starting materials shown are either o-dimethylaminomethyldiphenyl methanes or o-dibenzylaminomethyldiphenyl methanes. A "mixed" alkylamino compound such as o-N-methyl-N-benzylaminomethyldiphenyl methane may also be utilized. Under these circumstances, the benzyl group is the more labile and is eliminated upon ring closure or by catalytic hydrogenation.

It will be apparent to one skilled in the art that the aminomethyldiphenylmethanes may carry one or more common substituents in either one or both of the phenyl rings. Such common substituents are halogen (preferably chloro), lower alkoxy (preferably methoxy), lower alkyl (preferably methyl), hydroxy, lower alkanoyloxy, and obvious equivalent thereof. These substituents do not materially alter the biological properties of the unsubstituted compound making for differences in degree rather than kind. I therefore consider such ring substituted compounds as the full equivalent of the corresponding unsubstituted compounds of Formula I and within the concept of the composition aspect as set forth therein.

It will also be apparent to one skilled in the art that the carbon atom at the 5-position is asymmetric and thus the compounds depicted by the formulae and description contained herein are in actuality racemates. Resolution of the racemates into its optically active isomers may accordingly be effected by the standard techniques such as employment of an optically active acid, for example, in the case of the free bases. The optically active isomers are considered fully within the scope and purview of this invention.

The precursors for the starting materials of the process aspect of my invention, i.e., the o-disubstituted aminomethyldiphenylmethanes are prepared from the reaction of an appropriately substituted o-benzylbenzoic acid (XVI) and dimethylamine (or dibenzylamine or methylbenzylamine). Heating these two reagents together at temperatures above 100° C. permits the reaction to proceed with concomitant removal of water and results in the formation of an intermediate amide (XVII) which is reduced with lithium aluminum hydride, for example,

to yield the requisite o-disubstituted aminomethyldiphenylmethane (XVIII). This sequence of reactions is illustrated as follows:



In this reaction R_1 and R_2 represent methyl or benzyl. It is apparent that conversion of the benzylbenzoic acid (XVI) to its acid chloride followed by treatment with the secondary amine represents an alternate and obviously equivalent method for preparing XVII. The benzylbenzoic acids (XVI) are prepared by methods fully described in the art which includes those benzylbenzoic acids having nuclear substituents as set forth above. Thus in order to prepare a tangible embodiment of this invention as represented by Formula I but including a substituent on one or both of the aromatic rings, the correspondingly substituted benzylbenzoic acid is utilized.

As set forth in the statement of concept of the tangible embodiment of the invention, the compositions contemplated herein are bases, acid addition salts and quaternary ammonium salts thereof. The acid addition salts are preferably the non-toxic pharmaceutically acceptable salts of the bases with mineral acids such as hydrochloric acid. Also contemplated are salts with organic acids such as maleic and the like. These salts are prepared by standard methods such as mixing equivalent quantities of the base and the acid in a solvent in which the salt is insoluble. The salt is removed therefrom by filtration and is purified by recrystallization from a polar solvent like ethyl acetate or alcohol-ether. These acid addition salts have inherently the same biological properties as the free bases but provide a more convenient form for physically handling and formulating the bases.

The quaternary salts contemplated are benzyl and lower alkyl and phenyl lower alkyl quaternary salts with the anion being non-toxic and pharmaceutically acceptable. Representative of such anions are halide (chloride, bromide), sulfate and the like. The quaternary salts are prepared either as described heretofore or in the standard fashion by mixing a solution of the tertiary amine and a lower alkyl halide or sulfate in a solvent in which the quaternary salt is insoluble such as ether. The quaternary salt is removed by filtration and purified in a standard manner.

The following examples are illustrative of the preparation of the tangible embodiments of this invention. This invention is not limited to such examples but only by the appended claims and the obvious equivalents thereof taught herein.

PREPARATION 1

o-Benzyl-N,N-dimethylbenzamide

Melt o-benzylbenzoic acid. Bubble dimethylamine through the melt for 2–3 hours. Cool, triturate the solids with ether and filter. Wash the ether with dilute hydrochloric acid, then with water and then with 10% sodium carbonate solution. Dry the ether over sodium sulfate and evaporate to a residue consisting of the amide of this example.

PREPARATION 2

o-Benzyl-N,N-dibenzylbenzamide

To a solution of o-benzylbenzoyl chloride in anhydrous benzene, add dropwise a solution of dibenzylamine in anhydrous benzene (slight excess of dibenzylamine). Stir for 1 hour. Extract the reaction mixture with 10% sodium carbonate solution then with water and then with dilute hydrochloric acid. Dry and evaporate to a residue consisting of the amide of this example.

PREPARATION 3

o-Dimethylaminomethyldiphenylmethane

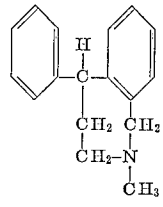
Suspend 16 g. of lithium aluminum hydride in 500 ml. of anhydrous ether and add dropwise, a solution of 38 g. of o-benzyl-N,N-dimethylbenzamide (from Preparation 1) in 100 ml. of ether. Reflux for 6 hours, cool and pour into a cold 15% sodium hydroxide solution. Separate the ether layer and wash the aluminum salts with ether. Dry the ether solution and evaporate to a residue. Distill in vacuo obtaining the compound of this example, 36 g., B.P. 109–112° C. (0.5 mm.).

In similar fashion, by utilizing the compound of Preparation 2 in the above procedure, there is obtained o-dibenzylaminomethyldiphenylmethane.

Nuclear substituted analogs of the compound of this example are prepared from the correspondingly substituted benzylbenzoic acids such as, for example, o-(p-chlorobenzyl)-benzoic acid which as per Preparations 1 and 3 give rise to o-dimethylaminomethyl-p'-chlorodiphenylmethane.

EXAMPLE 1

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



While stirring a solution of potassium amide (prepared from 4.0 g. of potassium in 400 ml. of liquid ammonia) add 22.5 g. of o-dimethylaminomethyldiphenyl methane (from Preparation 3). Stir for 30 minutes and then add 13.5 g. of β-dimethylaminoethyl chloride. Allow the ammonia to evaporate. Add water and extract the mixture with ether. Dry the ether solution, concentrate and distil the residue in vacuo obtaining α-(β-dimethylaminoethyl) - o - dimethylaminomethyldiphenyl methane, B.P. 142–147° C./0.5–1.0 mm.

Dissolve 3.3 g. of the product obtained above in 5.4 ml. of water containing 1.95 g. of concentrated hydrochloric acid. Evaporate the solution to dryness and heat the mono-hydrochloride at 270–290° C. until the evolution of gas (trimethylamine) ceases. Dissolve the residue in dilute hydrochloric acid, make alkaline with 10% aqueous sodium carbonate solution and extract with ether. Dry the ether solution and concentrate to a residue. Crystallize from petroleum ether obtaining the compound of this example, M.P. 74–75° C.

An alternate procedure for preparing the benzazepine of this example is as follows:

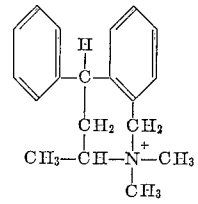
Suspend sodamide (from 2.5 g. of sodium) in 400 ml. of liquid ammonia and add 22.5 g. of o-dimethylaminomethyldiphenyl methane. Stir for 30 minutes and then add 18.5 g. of β-bromoethyl ether. Allow the ammonia to evaporate and then add 500 ml. of water. Extract with ether, dry the extracts, concentrate and distil in vacuo obtaining α - (β-ethoxyethyl)-o-dimethylaminomethyldiphenyl methane, B.P. 145–149° C./1 mm.

Dissolve 21.9 g. of the product obtained upon distillation in 125 ml. of 48% hydrobromic acid and reflux for 22–24 hours. Concentrate in vacuo to a residue and crystallize from ethanolether obtaining 5-phenyl-2,2-dimethyl-2,3,4,5-tetrahydro-1H-2-benzazepinium bromide, M.P. 250–253° C.

Pyrolyze the quaternary salt by heating at 300–350° C. under vacuum (1–5 mm.) until no more distillate is formed. The distillate (B.P. 185–230° C./1–5 mm.) is crystallized from petroleum ether, M.P. 74–75° C. to yield the compound of this example.

EXAMPLE 2

5-phenyl-2,2,3-trimethyl-2,3,4,5-tetrahydro-1H-2-benzazepinium chloride



Suspend sodamide (from 3.72 g. of sodium) in 200 ml. of liquid ammonia and add 31.7 g. of o-dimethylaminomethyldiphenyl methane (Preparation 3). Stir the red solution for 30 minutes and then add 17.1 g. of propylene oxide. Stir and allow the ammonia to evaporate. Add ice water and extract the mixture with ether. Dry the ether solution and distil collecting that fraction boiling at 166–167° C. (1.6 mm.) which consists of α-(2-hydroxypropyl)-o-dimethylaminomethyldiphenyl methane. Upon recrystallization from petroleum ether this substance melts at 91.5–92.5° C.

Dissolve 11.5 g. of the hydroxypropyl intermediate prepared above in 100 ml. of anhydrous benzene. Cool and slowly add 6 g. of thionyl chloride. Reflux for 30 minutes and concentrate to dryness in vacuo. Crystallize the residue from ethanol-ether to obtain α-(2-chloropropyl)-o-dimethylaminomethyldiphenyl methane hydrochloride, M.P. 155–156° C.

Treat the hydrochloride with aqueous sodium hydroxide and extract with ether. Dry the ether solution and concentrate to a residue. Heat the residue at 180–190° C. for 10 minutes and crystallize from ethanol-ether obtaining the quaternary chloride of this example, M.P. 246–249° C.

EXAMPLE 3

α-(β-Ethoxyethyl)-o-dibenzylaminomethyldiphenyl methane

The compound of this example is prepared via the first step in the alternate procedure of Example 1 utilizing postassium amide (from 2 g. of potassium), 250 ml. of liquid ammonia, 18.8 g. of o-dibenzylaminomethyldiphenyl methane and 7.7 g. of β-bromoethyl ether.

EXAMPLE 4

5-phenyl-2,2-dibenzyl-2,3,4,5-tetrahydro-1H-2-benzazepinium bromide

Dissolve 12.5 g. of the compound of Example 3 in 100 ml. of 48% hydrobromic acid and reflux for 20–24 hours. Concentrate to a residue in vacuo and crystallize from ethanol-ether to obtain the quaternary salt of this example.

EXAMPLE 5

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

Pyrolize the quaternary salt of Example 4 at 300–320° C. collecting that distillate boiling at 195–225° C./2.5 mm. The distillate cools to a glassy solid consisting of the compound of this example.

EXAMPLE 6

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

Hydrogenate 3.5 g. of the compound of Example 5 in 100 ml. of methanol in which is suspended 3.5 g. of

palladium charcoal catalyst (5%) by shaking in a Parr hydrogenator under 60 lbs. per sq. in. of hydrogen until the calculated theoretical quantity of hydrogen (1 mole per mole of 5-phenyl-2-benzyl-2,3,4,5-tetrahydro-1H-benzazepine) has been absorbed. Remove the catalyst by filtration and concentrate to a residue consisting of the secondary amine of this example. The benzazepine so formed is concentrated to its maleate salt by dissolving equivalent quantities of the benzazepine and maleic acid in ethyl acetate and crystallizing the salt therefrom.

EXAMPLE 7

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

To a stirred mixture of 4.5 g. of the compound of Example 6, 100 ml. of anhydrous benzene and 2.0 g. of anhydrous sodium bicarbonate, add 4.0 g. of 2-phenethylbromide. Reflux and stir for 16–24 hours and add water. Separate the benzene layer, dry and concentrate in vacuo. The residue is an oil which slowly crystallizes yielding the compound of this example.

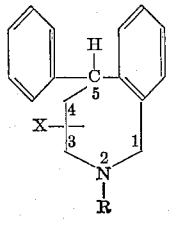
EXAMPLE 8

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

Pyrolize the quaternary salt of Example 2 at 300–320° C. collecting that distillate boiling at 190–206° C./4.7 mm. Upon cooling, the distillate forms a glassy solid consisting of the compounds of this example. A maleate salt prepared from the base and maleic acid in a known manner melts at 119–121° C.

I claim:

1. A member of the group consisting of a benzazepine having the formula:



and the non-toxic acid addition salts and quaternary salts thereof wherein X is a member of the group consisting of H and methyl and R is a member of the group consisting of H, lower alkyl and phenyl lower alkyl.

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

3. A non-toxic acid addition salt of 2-methyl-5-phenyl-2,3,4,5-tetrahydro-1H-2-benzazepine.

4. 5-phenyl-2,2,3-trimethyl-2,3,4,5 - tetrahydro-1H-2-benzazepinium chloride.

5. 5-phenyl-2,2-dibenzyl-2,3,4,5 - tetrahydro-1H-2-benzazepinium bromide.

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

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

8. 5-phenyl-2-phenethyl-2,3,4,5 - tetrahydro-1H-2-benzazepine.

9. 5-phenyl-2,2-dimethyl-2,3,4,5-tetrahydro-1H-2-benzazepinium bromide.

10. 5-phenyl-2,3 - dimethyl-2,3,4,5 - tetrahydro-1H-2-benzazepine.

11. In the process for preparing a 5-phenyl-2,3,4,5-tetrahydro-1H-2-benzazepine, the acid addition salts and quaternary ammonium salt thereof, the step which comprises heating at an elevated temperature a member of the group consisting of an o-R_1R_2-aminoethyldiphenylmethane and the acid addition salts thereof, having a lower alkyl group of at least two carbon atoms attached to the methane carbon atoms, the β-carbon atom of said alkyl group bearing a substituent selected from the group consisting of R_1R_2-amino and halogeno, wherein R_1 and R_2 are members of the group consisting of methyl and benzyl until substantial transformation into a tetrahydro-benzazepine compound is effected.

References Cited by the Examiner

UNITED STATES PATENTS

2,520,264	8/1950	Walter	260—239
2,684,962	7/1954	Walter	260—239
2,956,072	10/1960	Bloom	260—456
2,962,514	11/1960	Carbon et al.	260—456

NICHOLAS S. RIZZO, *Primary Examiner.*