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5-(BASIC SUBSTITUTED)-DIBENZODIAZEPINES

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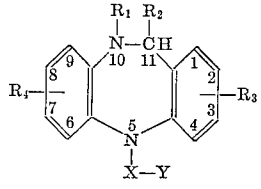
11 Claims. (Cl. 260—239)

This application is a continuation-in-part of an application filed by us in the United States Patent Office on Aug. 22, 1962, Ser. No. 218,557, now abandoned, the latter being in turn a continuation-in-part of our patent application Ser. No. 57,109, filed Sept. 20, 1960, now abandoned, and also a continuation-in-part of our patent applications Ser. Nos. 57,122 and 57,141, both filed on Sept. 20, 1960, and both now abandoned.

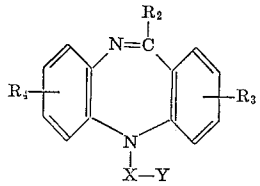
This invention relates to novel heterocyclic nitrogen-containing compounds. More specifically, it relates to 5-(basic substituted)-10,11-dihydro-5H-dibenzo[b,e][1,4]-diazepines having the general formula



(I)

and salts, such as the acid addition salts or the quaternary ammonium salts thereof. In the above Formula I the letter symbols have the following meanings: X represents alkylene containing between 2 and 3 inclusive carbon atoms, and more specifically, X represents ethylene, propylene, or isopropylene; Y is a member selected from the class consisting of dialkylamino having between 2 and 4 inclusive carbon atoms, pyrrolidino, piperidino, morpholino, piperazino, (4'-methyl)piperazino, and (4'-ethyl)piperazino; R_1 is a member of the class consisting of hydrogen, methyl, ethyl, formyl, acetyl, benzyl, and benzoyl; R_2 is a member of the class consisting of hydrogen, methyl, ethyl, and phenyl; and R_3 and R_4 represent, interchangeably, a member of the class consisting of hydrogen, chlorine, methyl, ethyl, methoxy, ethoxy, methylthio, and ethylthio.

The new compounds of this invention are obtained by effecting hydrogenation of the corresponding 5-(basic substituted) - 5H - dibenzo[b,e][1,4]diazepines, followed, if necessary, by acylation, alkylation or aralkylation of the hydrogenation product in position 10. The starting materials to be hydrogenated in accordance with this process are represented by the general formula:



(II)

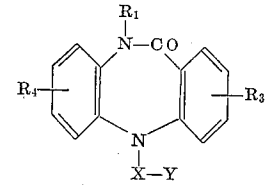
In the above Formula II the letter symbols X, Y, R_2, R_3, and R_4 have the same meaning as identified before. The hydrogenation of the compounds represented by Formula II to obtain the compounds of Formula I may be effected by using hydrogen and a metal catalyst (such as a nickel or copper chromite catalyst) or by using complex metal hydrides, particularly lithium-aluminium hydride. The latter technique is particularly advantageous.

As disclosed above, the symbol R_1 of the products having the Formula I may be hydrogen, methyl, ethyl,

formyl, acetyl, benzyl, or benzoyl. It will be understood that while in the hydrogenation product R_1 is hydrogen, the hydrogenated compound may subsequently be acylated, alkylated, or benzylated, to introduce in the 10-position an R_1 residue which is not hydrogen, e.g. by metallizing the hydrogenation product and thereafter reacting the metallized compound with a corresponding carboxylic acid halide, a lower alkyl halide or with a benzyl halide.

The starting materials having the Formula II can be obtained by effecting ring closure or cyclization of the corresponding N—(—X—Y)-acylamino-diphenylamines in the presence of a suitable condensing agent such as polyphosphoric acid, as more fully described in our co-pending application Ser. No. 160,382, filed on Oct. 31, 1961, now U.S. Patent No. 3,129,236, which is a continuation-in-part of an application filed on Jan. 19, 1960, Ser. No. 3,275 and now abandoned.

Those products of Formula I according to this invention, wherein R_2 denotes hydrogen, can also be obtained by effecting reduction of the corresponding 5-(basic substituted)-10,11-dihydro-11-oxo-5H - dibenzo[b,e][1,4]diazepines. The starting materials to be reduced according to this second method are represented by the general formula:

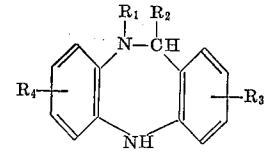


(III)

In the above Formula III, the letter symbols X, Y, R_1, R_3 and R_4 have the same meaning as identified above. The reduction of the —CO— group of the compounds represented by Formula III to obtain the heterocyclic nitrogen-containing compounds of Formula I may be effected by the usual techniques for the reduction of an amide group, e.g. by reaction with metal hydrides, by reaction with hydrogen (especially in the presence of a catalyst, such as copper chromite), or by electrolytic reduction. We have found the use of lithium-aluminium hydride to be particularly advantageous.

As disclosed above, the symbol R_1 of the starting material having the Formula III may be hydrogen, methyl, ethyl, formyl, acetyl, benzyl, or benzoyl. If the symbol R_1 of the starting compound is hydrogen, the final reduced compound may be subsequently acylated, alkylated, or aralkylated to introduce in the 10-position an R_1 residue which is not hydrogen, e.g. by metallizing the reduced compound and thereafter reacting the metallized compound with a corresponding carboxylic acid halide, a corresponding alkyl halide or with a benzyl halide.

Those products of Formula I according to this invention, wherein R_1 denotes methyl, ethyl, formyl, acetyl, benzyl, or benzoyl, can further be obtained by introducing a corresponding tertiary aminoalkyl residue into the corresponding 5-unsubstituted 10,11-dihydro-5H-dibenzo-[b,e][1,4]diazepines. The starting materials used in this third method are represented by the general formula:



(IV)

In the above Formula IV, the letter symbols R_1, R_2, R_3 and R_4 have the same meaning as identified above, but preferably, R_1 does not denote hydrogen. The introduc-

tion of the basic radical —X—Y in place of a hydrogen atom in the 5-position in compounds of Formula IV to obtain the compounds of Formula I may be effected in several ways of which the following techniques are exemplary:

(a) The Formula IV compound may be reacted with an ester of a tertiary aminoalkanol, this ester having the formula Z—X—Y, wherein X and Y have the meanings described above and Z represents an acid residue, particularly the acid residue of inorganic or organic acids such as hydrohalogen acids, sulfonic acids or carbonic acid. The reaction with esters of hydrohalogen acids or sulfonic acids is preferably carried out by prior or concurrent metallization of the Formula IV compound using a suitable condensation agent, particularly the alkali metals, their hydrides, amides, or other organic alkali metal compounds, e.g., sodium amide, sodium hydride, phenyl sodium, or tertiary butyl sodium. No condensing agent is necessary if the reaction is performed using a carbonic acid ester.

(b) The introduction of the basic radical —X—Y into the Formula IV compound may also take place in two steps. First, a halogen alkyl group of the formula —X—Hal is introduced into the Formula IV compound at the 5-position, e.g., by reaction with an ester of the corresponding halogen alkanol having the formula Z—X—Hal where Hal represents halogen and Z and X have the meanings described above, or by reaction with an alkylene oxide followed by esterification with a hydrohalogen acid. Second, the resulting halogen compound from the first step is reacted with a secondary amine of the formula H—Y or a corresponding tertiary derivative where Y has the meaning described above.

The compounds of the Formula I type are strong bases which may readily be converted to water soluble salts of non-toxic inorganic and organic acids. For example, suitable inorganic acid addition salts include the hydrochlorides, hydrobromides, sulfates, nitrates, and phosphates. Suitable organic acid addition salts may also be formed, e.g., the acetates, oxalates, malonates, succinates, maleates, tartrates, or toluene sulfonates. The mono- and diquaternary lower alkyl ammonium derivatives may also be prepared, for example, by reacting the bases with a quaternizing agent such as a dialkylsulfate, an alkyl halide, or a sulfonic acid alkyl ester. The quaternary ammonium derivatives of the Formula I compounds may also be obtained by utilizing as starting materials in the processes described above the quaternary ammonium derivatives of the Formula II or Formula III compounds, respectively.

The new 5-(basic substituted)-10,11-dihydro-5H-dibenzo-[b,e][1,4]diazepines according to the invention, including the bases (I) per se as well as the addition salts with non-toxic acids and the lower alkyl quaternary ammonium halides, sulfates, and sulfonates thereof, are useful as medicaments, and more specifically as antihistamines, anticonvulsants, antidepressants, and spasmolytics. They may be administered, for example, in the form of pharmaceutical preparations, which contain the new compound or a salt thereof with a pharmaceutical organic or inorganic solid or liquid carrier suitable for enteral, parenteral or topical administration. For making up the preparation, there can be employed substances which are compatible with the new compounds, such as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly or another known carrier for medicaments. The pharmaceutical preparations may be, for example, in the form of tablets, dragees, salves, creams or in liquid form as solutions, suspensions, or emulsions. If desired, they may be sterilized and/or contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure, or buffers. They may also contain other therapeutically useful substances. The preparations are obtained by the usual method employed in formulating pharmaceutical dosage forms.

The following non-limiting examples will further illustrate the invention:

Example 1

A solution of 1.40 g. of 5-γ-dimethylamino-propyl-5H-dibenzo[b,e][1,4]diazepine in 35 ml. of absolute tetrahydrofuran was added dropwise to 1.0 g. of lithium-aluminium hydride in 30 ml. of absolute tetrahydrofuran while stirring and over a period of 20 minutes. The mixture was heated for 3 hours under reflux and while stirring, whereupon excess lithium-aluminium hydride was destroyed with acetic ester and the reaction mixture evaporated to dryness in vacuo. The residue was distributed between water and ether. After separating out inorganic hydroxides by filtration, the basic product was isolated by extraction with acetic acid, precipitation with ammonia, and extraction of the free base with ether. 1.02 g. (72% of the theoretical yield) of 5-γ-dimethylamino-propyl-10,11-dihydro - 5H - dibenzo[b,e][1,4]diazepine with a melting point of 99–101° C. were obtained.

Example 2

By the same procedure as described in Example 1, 4.7 g. of 5-β-dimethylamino-ethyl-7-chloro - 10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine, in the form of solid prisms with a melting point of 114–116° C. (from ether/petroleum ether), were obtained from 6.3 g. of 5-β-dimethylamino - ethyl - 7 - chloro-5H-dibenzo[b,e][1,4]diazepine.

Example 3

Using the same procedure as described in Example 1, 4.5 g. of 5-γ-dimethylamino-propyl-7-chloro-10,11-dihydro-5H-dibenzo[b,e,][1,4]diazepine in the form of granular crystals with a melting point of 114–116° C. (from ether/petroleum ether) were obtained from 5.8 g. of 5-γ-dimethylamino - propyl - 7 - chloro-5H-dibenzo[b,e][1,4]diazepine.

Example 4

Using the same procedure as in Example 1, 2.9 g. of d,l-5-β-dimethylamino-ethyl-7-chloro - 10,11 - dihydro-11-methyl-5H-dibenzo[b,e][1,4]diazepine in the form of solid granules with a melting point of 104–106° C. (from ether/petroleum ether) were obtained from 4.3 g. of 5-β-dimethylamino-ethyl - 7 - chloro-11-methyl-5H-dibenzo[b,e][1,4]diazepine.

Example 5

A 20.0 g. quantity of 5-β-dimethylamino-ethyl-11-methyl-5H-dibenzo[b,e][1,4]diazepine was shaken in the presence of 4.0 g. of Raney nickel, 1.0 g. of palladium on carbon (5%) and 9.0 g. of potassium hydroxide beads in 140 ml. of methanol at room temperature under slight superatmospheric pressure in a hydrogen atmosphere until the absorption of hydrogen stopped.

After filtering off the catalyst with suction and after concentration in vacuo, the residue was distributed between ether and water, the etheral solution was washed with water and it was worked up in the usual manner. On recrystallization from ether/petroleum ether and with clarification with aluminium oxide, there were obtained 16.0 g. of d,l-5-β-dimethylamino-ethyl - 10,11 - dihydro - 11-methyl-5H-dibenzo[b,e][1,4]diazepine in the form of white prisms with a melting point of 75–76° C.

1.12 g. of dimethylsulfate were added to 2.5 g. of this product in 40 ml. of acetone. After standing for 6 hours, the substance was suction-filtered and recrystallized from isopropanol/acetic ether, 2.7 g. of the corresponding methosulfate being obtained in the form of prismatic needles with the melting point of 204–208° C.

4.5 g. of the d,l-5-β-dimethylamino-ethyl-10,11-dihydro-11-methyl-5H-dibenzo[b,e][1,4]diazepine obtained in the manner described above were heated with 30 ml. of acetic anhydride for 4 hours under reflux. After con-

centration in vacuo and dissolving the residue in water, the base was liberated with ammonia and taken up in either. The ethereal solution was worked up in the usual manner.

By recrystallization from acetone/petroleum ether and while clarifying with aluminium oxide, there were obtained 3.8 g. of the corresponding 10-acetyl compound in the form of weakly yellowish prisms having the melting point of 126–128° C.

By treatment with benzoyl chloride in pyridine at room temperature and working up in the usual manner, there was obtained the benzoyl derivative of d,1-5-β-dimethylamino-ethyl-10,11-dihydro-11-methyl - 5H - dibenzo[b,e][1,4]diazepine, melting point of 97.5–98° C. (from ether/petroleum ether).

Example 6

Using the same procedure as in Example 5, 27.6 g. of d,1-5-γ-dimethylamino-propyl-10,11-dihydro-11 - methyl-5H-dibenzo[b,e][1,4]diazepine were obtained from 33.0 g. of 5-γ-dimethylamino-propyl-11-methyl-5H-dibenzo-[b,e][1,4]diazepine, the former substance being in the form of a yellowish viscous oil with a boiling point of 158–164° C./0.04 mm. Hg, which could be crystallized from petroleum/ether with the melting point of 86–88° C.

Using the same procedure as in Example 5, the methosulfate of this base was obtained in the form of white prisms with the melting point of 203–204° C. (from methanol/ether).

The 10-acetyl compound with the boiling point of 175–185° C./0.07 mm. Hg prepared according to Example 5 could be crystallized from ether/petroleum ether with the melting point of 81–82° C. The hyrochloride thereof showed a melting point of 154–155° C. (from acetone/acetic ester).

Example 7

From 10.0 g. of 5-β-dimethylamino-ethyl-11-phenyl-5H-dibenzo[b,e][1,4]diazepine, there was obtained by the same procedure as in Example 5, 7.6 g. of d,1-5-β-dimethylamino-ethyl-10,11-dihydro-11-phenyl-5H - dibenzo-[b,e][1,4]diazepine in the form of compact prisms with the melting point of 159–160° C. (from acetone/petroleum ether).

From 2.9 g. of the above base, using the same procedure as in Example 5, there were obtained 3.7 g. of methosulfate in the form of white prisms with the melting point of 214–218° C. (from methanol/ether).

Example 8

Using the same procedure as in Example 5, a distillable oil with the boiling point of 205–210° C./0.01 mm. Hg was obtained from 14.0 g. of 5-γ-dimethylamino-propyl-11-phenyl-5H-dibenzo[b,e][1,4]diazepine, and on being crystallized from ether/petroleum ether, this oil yielded 8.7 g. of d,1-5-γ-dimethylamino-propyl-10,11-dihydro-11-phenyl-5H-dibenzo[b,e][1,4]diazepine in the form of colourless prismatic needles having the melting point of 125–128° C.

Using the same procedure as in Example 5, 2.8 g. of methosulfate with the melting point of 217–219° C. (from methanol/acetone) were obtained from 2.5 g. of the said base.

Example 9

Following the procedure of Example 1, there was obtained from 8.7 g. of 5-β-dimethylamino-ethyl-8,11-dimethyl-5H-dibenzo[b,e][1,4]diazepine, a yield of 6.6 g. of 5-β-dimethylamino-ethyl-8,11-dimethyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine, having a boiling point of 164–165° C./0.05 mm. Hg.

Example 10

Following the procedure of Example 1, there are obtained from 5-β-(N'-methyl-piperazino-ethyl)-11-methyl-5H-dibenzo[b,e][1,4]diazepine, the product 5-β-(N'-methyl-piperazino-ethyl)-11-methyl-10,11 - dihydro - 5H-dibenzo[b,e][1,4]diazepine, having a melting point of 81–83° C. (from ether/petroleum ether) in a yield of 80% of the theory.

Example 11

Following the procedure of Example 1, there was obtained from 4-methoxy-5-β-dimethylamino-ethyl-11-methyl-5H-dibenzo[b,e][1,4]diazepine, the product 4-methoxy-5-β-dimethylamino-ethyl-11-methyl-10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine, having a melting point of 101–103° C. (from acetone/petroleum ether) in a yield of 85% of the theory.

Example 12

Following the procedure of Example 1, there was obtained from 2-methoxy-5-β-dimethylamino-ethyl-11-methyl-5H-dibenzo-[b,e][1,4]diazepine, the product 2-methoxy-5-β-dimethylamino-ethyl-11-methyl-10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine, having a melting point of 74–76° C. (from petroleum ether) in a yield of 73% of the theory.

Example 13

Following the procedure of Example 1, there was obtained from 5-γ-morpholino-propyl-11-methyl-5H-dibenzo[b,e][1,4]diazepine, the product 5-γ-morpholino-propyl-11-methyl-10,11-dihydro-5H - dibenzo[b,e][1,4]diazepine, having a melting point of 84–86° C. (from acetone/petroleum ether) in a yield of 80% of the theory.

Example 14

Following the procedure of Example 1, there was obtained from 5-β-piperidino-ethyl-11-methyl-5H-dibenzo-[b,e][1,4]diazepine, the product 5-β-piperidino-ethyl-11-methyl-10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine, having a melting point of 80–83° C. and 117–119° C. (from petroleum ether) in a yield of 71% of the theory.

Example 15

Using the same procedure as in Example 1, 5 - β - dimethylaminoethyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine in the form of a yellowish oil of the boiling point 162–164° C./0.03 mm. Hg was obtained in a yield of 75% of the theoretical from 5 - β - dimethylaminoethyl - 5H - dibenzo[b,e][1,4]diazepine.

Example 16

The base obtained according to Example 15 was treated with acetanhydride by the same procedure as in Example 5, obtaining 5 - β - dimethylamino - ethyl - 10 - acetyl-10,11 - dihydro - 5H - dibenzo[b,e][1,4] - diazepine, melting point of 113–114° C. (from ether/petroleum ether), in a yield of 65% of the theory.

Example 17

2.8 g. of the base obtained according to Example 15 were dissolved in 25 ml. of absolute dioxane, mixed with 0.5 g. of powdery sodium amide and heated for 1 hour at reflux. Then 0.6 g. of monochloromethane were added and the whole heated for another 16 hours under reflux. The reaction mixture was evaporated in vacuo to dryness, the residue distributed between ether and water and the base isolated in the usual way. 1.8 g. of 5 - β - dimethylaminoethyl - 10 - methyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine were obtained as a thick oil of boiling point 165–167° C./0.02 mm. Hg. The methosulfate can be obtained from acetone in crystalline form, melting point of 177–182° C.

Example 18

Using the same procedure as in Example 17 but substituting benzylchloride for monochloromethane, 5 - β-dimethylamino - ethyl - 10 - benzyl - 10,11 - dihydro-5H - dibenzo[b,e][1,4]diazepine was obtained as a thick oil of boiling point 212–214° C./0.08 mm. Hg. in a yield of 63% of the theory. The methosulfate, which can be

made to crystallize out of acetone, showed the melting point of 138–143° C.

Example 19

The product of Example 1 was methylated according to Example 17, obtaining 5 - γ - dimethylamino - propyl-10 - methyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4] diazepine as a thick oil of the boiling point of 164–165° C./0.01 mm. Hg in a yield of 68% of the theory. The methosulfate could be obtained only in the form of its aqueous solution.

Example 20

The product of Example 1 was benzylated according to Example 18, obtaining 5 - γ - dimethylamino - propyl-10 - benzyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4] diazepine in a yield of 64% of the theory in the form of a thick oil of the boiling point of 207° C./0.01 mm. Hg, which crystallized on being allowed to stand, melting point of 45–47° C. (from cold petroleum ether).

Example 21

A solution of 3.97 g. of 5 - β - dimethylamino - ethyl-10,11 - dihydro - 11 - oxo - 5H - dibenzo[b,e][1,4] diazepine in 60 ml. of tetrahydrofuran was added dropwise within 20 minutes to 1.7 g. of lithium-aluminium hydride in 30 ml. of absolute tetrahydrofuran while stirring. The mixture was then heated for 3 hours under reflux while continuing stirring, whereupon excess lithium-aluminium hydride was destroyed with acetic ester and the reaction mixture was brought to dryness in vacuo. The residue was distributed between water and ether. After separating out inorganic hydroxides by filtration, the basic product was isolated by extraction with acetic acid, precipitation with ammonia, and extraction of the free base with ether. 3.4 g. (90% of the theoretical yield) of 5 - β - dimethylamino - ethyl - 10,11 - dihydro - 5H-dibenzo[b,e][1,4] diazepine were obtained in the form of a yellowish oil having the boiling point of 162–164° C./0.03 mm. Hg.

Example 22

3.15 g. of 5 - β - dimethylamino - ethyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine, which had been obtained as in Example 1, were boiled under reflux for 4 hours with 20 ml. of acetic anhydride. After dilution with water and being left to stand, the base was liberated from the clear solution with ammonia and isolated by extraction with ether. By recrystallization from ether/petroleum ether, 2.6 g. of the corresponding 10 - acetyl compound with the melting point of 113–114° C. were obtained.

Example 23

Using the same procedure as in Example 21, and employing a solution of 3.0 g. of 5 - γ - dimethylamino-propyl - 10,11 - dihydro - 11 - oxo - 5H - dibenzo[b,e][1,4]diazepine in 60 ml. of absolute tetrahydrofuran and a suspension of 1.2 g. of lithium-aluminium hydride in 30 ml. of tetrahydrofuran, 2.15 g. (75% of the theoretical yield) of 5 - γ - dimethylamino - propyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine were obtained in the form of greenish, lustrous granules with the melting point of 99–101° C. (from ether/petroleum ether 1:4).

Example 24

Using the same procedure as in Example 21, and from 8.8 g. of 5 - β - dimethylamino - ethyl - 7 - chloro - 10,11-dihydro - 11 - oxo - 5H - dibenzo[b,e][1,4]diazepine, there were obtained 6.2 g. of 5 - β - dimethylamino-ethyl - 7 - chloro - 10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine in the form of prisms with the melting point of 114–116° C. (from ether/petroleum ether).

Example 25

Using the same procedure as in Example 21 and from 9.0 g. of 5 - γ - dimethylamino - propyl - 7 - chloro-10,11 - dihydro - 11 - oxo - 5H - dibenzo[b,e][1,4]diazepine, there were obtained 6.1 g. of 5 - γ - dimethylamino - propyl - 7 - chloro - 10,11 - dihydro - 5H - dibenzo[b,e][1,4] diazepine in the form of pale yellow granules with the melting point of 114–116° C. (from ether/petroleum ether).

Example 26

Using the same procedure as in Example 21 and from 8.5 g. of 5 - β - dimethylamino - ethyl - 10 - methyl-10,11 - dihydro - 11 - oxo -5H - dibenzo[b,e][1,4]diazepine, there were obtained 6.6 g. of 5 - β - dimethylamino - ethyl - 10 - methyl - 10,11 - dihydro - 5H - dibenzo[b,e][1,4]diazepine as a thick oil with the boiling point of 165–167° C./0.02 mm. Hg.

The methosulfate initially precipitated as an oil from equimolar quantities of this base and acid-free dimethylsulfate in benzene solution was obtained in crystalline form by treatment with acetone, melting point of 177–182° C.

Example 27

Using the same procedure as in Example 21 and from 15.47 g. of 5-γ-dimethylamino-propyl-10-methyl-10,11-dihydro-11-oxo - 5H - dibenzo[b,e][1,4]diazepine, there were obtained 11.23 g. of 5-γ-dimethylamino-propyl-10-methyl-10,11-dihydro-5H-dibenzo-[b,e][1,4]diazepine as a thick oil with the boiling point of 164–165° C./0.01 mm. Hg.

Example 28

Using the same procedure as in Example 21 and from 10.02 g. of 5-β-dimethylamino-ethyl-10-benzyl-10,11-dihydro-11-oxo-5H-dibenzo[b,e][1,4]diazepine, there were obtained 7.87 g. of 5-β-dimethylamino-ethyl-10-benzyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine as a thick oil with the boiling point of 212–214° C./0.08 mm. Hg.

The methosulfate was prepared in the same way as set out in Example 26, which methosulfate was caused to crystallize from acetone with the melting point of 138–143° C.

Example 29

Using the same procedure as in Example 21 and from 8.65 g. of 5-γ-dimethylamino-propyl-10-benzyl-10,11-dihydro-11-oxo-5H-dibenzo[b,e][1,4]diazepine, there were obtained 6.7 g. of 5-γ-dimethylamino-propyl-10-benzyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine in the form of a thick oil with the boiling point of 207° C./0.01 mm. Hg, this substance crystallizing on standing and having the melting point of 45–47° C. (from cold petroleum ether).

By proceeding in analogous manner as described in the precedent examples, the following further compounds in accordance with Formula I or salts thereof, respectively, were obtained:

Example 30.—5-β-dimethylamino-ethyl-8-methyl - 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine, melting point of 75–78° C.

Example 31.—5-β-dimethylamino-ethyl-8-methyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine, melting point of 107–109° C.

Example 32.—5-β-dimethylamino-ethyl-7-methoxy-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine, boiling point of 162–164° C./0.03 mm. Hg.

Example 33.—5-β-dimethylamino-ethyl-7-chloro - 10-methyl-10,11-dihydro - 5H - dibenzo[b,e][1,4]diazepine, boiling point of 161° C./0.05 mm. Hg.

Example 34.—5-β-pyrrolidino-ethyl-7-chloro-10-methyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine, boiling point of 181–185° C./0.03 mm. Hg; melting point of the maleate: 130–148° C.

Example 35.—5-β-morpholino-ethyl-7-chloro-10-methyl-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine maleate, melting point of 170–173° C.

Example 36.—5-β-(4'-methyl)piperazino-ethyl-7-chloro-10-methyl-10,11-dihydro-5H - dibenzo[b,e][1,4]diazepine dimaleate, melting point of 194–197° C.

Example 37.—5-β-dimethylamino-ethyl-7-chloro-10,11-dihydro-11-methyl-5H-dibenzo[b,e][1,4]diazepine, melting point of 74–78° C.

Example 38.—5-β-dimethylamino - ethyl-7-methylthio-10,11-dihydro - 5H-dibenzo[b,e][1,4]diazepine, boiling point of 193–196° C./0.04 mm. Hg.

Production of tablets

For the manufacture of tablets, the products of the present invention, preferably in the form of the hydrochlorides or of the maleates, can be mixed with lactose and granulated with water, 0.5% sodium alginate or 1% gelatine solution. The dried granulate can be compressed into tablets in the presence of about 5% of talcum, 5% of corn starch and 0.1% of magnesium stearate. In this way, there are obtained, e.g. tablets of the following composition:

	mg.
5-β-dimethylamino-ethyl-7-chloro - 10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine	20
Lactose	160
Corn starch	10
Talcum	10
Magnesium stearate	0.2

These 0.200 g. tablets possess antidepressant action and can be administered orally in appropriate indications.

Production of solutions

Injectable solutions are obtained, for example, by dissolving in bidistilled water the products of the present invention in the form of their hydrochlorides or other salts and by adding sodium chloride or glucose until isotonic concentration is reached. The solutions are filtered free of germs, filled into ampoules and sterilized for 30 minutes at 120° C. in the autoclave. In this way, there is obtained, for example, an injectable solution of the following composition:

5-β-dimethylamino-ethyl-7-chloro-11-methyl - 10,11-dihydro-5H - dibenzo[b,e][1,4]diazepine hydrochloride	mg.	5
Sodium chloride	mg.	41.5
Bidistilled water, up to	ml.	5

This solution, when administered intravenously, possesses antidepressant action and can be used in appropriate indications.

Production of suppositories

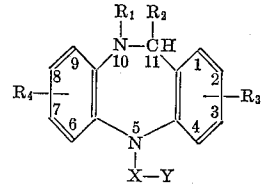
Suppositories are obtained, for example, by grinding to a fine powder the products of the present invention in the form of bases or salts, by mixing intimately with a molten suppository mass (e.g. Oleum Cacao, Witten mass and the like) if necessary in the presence of paraffin oil, by pouring the mixture into moulds and by allowing to cool at low temperature. In this way, there are obtained, for example, suppositories of the following composition:

	mg.
5-β-dimethylamino-ethyl-10,11-dihydro - 5H - dibenzo[b,e][1,4]diazepine	5
Paraffin oil	95
Oleum Cacao	210

These suppositories show antihistamine action and can be administered in appropriate indications.

We claim:

1. A compound selected from the group consisting of a 5-(basic substituted)-10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine of the formula:



wherein X represents alkylene having between 2 and 3 inclusive carbon atoms; Y is a member of the class consisting of dialkylamino having between 2 and 4 inclusive carbon atoms, pyrrolidino, piperidino, morpholino, piperazino, (4'-methyl)piperazino, and (4'-ethyl)piperazino; R_1 is a member of the class consisting of hydrogen, methyl, ethyl, formyl, acetyl, benzyl, and benzoyl; R_2 is a member of the class consisting of hydrogen, methyl, ethyl, and phenyl; and R_3 and R_4 represent, interchangeably, a member of the class consisting of hydrogen, chlorine, methyl, ethyl, methoxy, ethoxy, methylthio, and ethylthio; and non-toxic therapeutically useful acid addition salts and lower alkyl quaternary ammonium halides, sulfates, and sulfonates thereof.

2. 5-β-dimethylamino-ethyl-10,11 - dihydro-5H-dibenzo-[b,e][1,4]diazepine.

3. 5-β-dimethylamino-ethyl-10-methyl-10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine.

4. 5-γ-dimethylamino-propyl - 10,11 - dihydro-5H-dibenzo-[b,e][1,4]diazepine.

5. 5-β-dimethylamino-ethyl-7-chloro - 10,11 - dihydro-5H-dibenzo[b,e][1,4]diazepine.

6. 5-β-dimethylamino-ethyl-7-chloro-10-methyl - 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine.

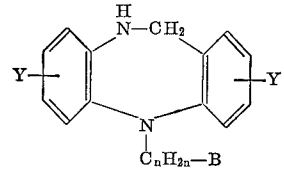
7. 5-β-dimethylamino-ethyl-7-chloro - 10,11 - dihydro-11-methyl-5H-dibenzo[b,e][1,4]diazepine.

8. 5-β-dimethylamino-ethyl-10-benzoyl - 10,11 - dihydro-11-methyl-5H-dibenzo[b,e][1,4]diazepine.

9. 5-γ-dimethylamino - propyl-10,11-dihydro-11-methyl-5H-dibenzo[b,e][1,4]diazepine.

10. 5-β-dimethylamino - ethyl-10,11-dihydro-11-phenyl-5H-dibenzo[b,e][1,4]diazepine.

11. A member selected from the group consisting of a compound of the formula:



and the pharmacologically useful acid addition salts thereof, wherein each Y is independently selected from the group consisting of hydrogen, chlorine, methyl, ethyl, methoxy, and ethoxy, *n* is an integer from 2 to 3 inclusive, and B is selected from the group consisting of dialkylamino having from 2 to 4 carbon atoms inclusive, pyrrolidino, piperdino, and morpholino.

No references cited.

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