

1.126.353



PATENT SPECIFICATION

NO DRAWINGS

1.126.353

Date of Application and filing Complete Specification: 13 Aug., 1965.

No. 3327/68.

Application made in United States of America (No. 391,732) on 24 Aug., 1964.

(Divided out of No. 1,126,352).

Complete Specification Published: 5 Sept., 1968.

© Crown Copyright 1968.

Index at acceptance:—C2 C(1E6K4, 1F2C2, 1F2D3)

Int. Cl.:—C 07 d 57/02

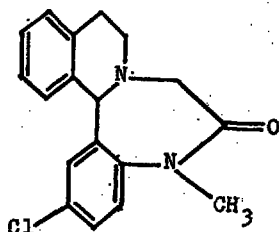
COMPLETE SPECIFICATION

Isoquinolinobenzodiazepine Derivatives

We, SANDOZ LTD., of Lichtstrasse 35, Basle, Switzerland, a Swiss Body Corporate, 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:—

The present invention relates to a new heterocyclic base, its acid addition salts and processes for their production.

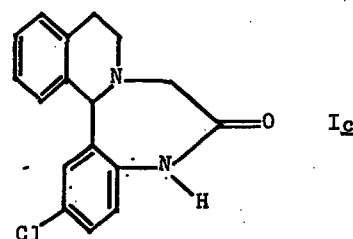
The present invention provides (+)-2-chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1-d]benzo - [1,4]-diazepin-6-one and its acid addition salts; said free base has the formula



I

Processes are described below for producing the racemate of the free base of the invention; the required (+)-isomer is obtained in manner known *per se*, or it may be produced via an optically active intermediate in the first instance.

The present invention further provides a process for the production of the compound of formula I above or an acid addition salt thereof, which comprises heating the compound of the formula Ic (which is described and claimed in Patent Specification No. 34751/65 (Serial No. 1,126,352))



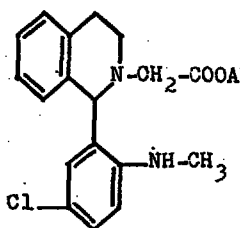
Ic

30

with methyl chloride, methyl bromide or methyl iodide in an inert solvent and in the presence of a base, and, when an acid addition salt is required, reacting with an organic or inorganic acid, separation and isolation of the required (+)-isomer being effected in manner known *per se*.

As pointed out in specification No. 34751/65 (Serial No. 1,126,352), the reaction of compound Ic with methyl bromide, iodide or chloride is effected in manner known *per se* in an inert organic solvent, e.g. dioxane, dimethyl formamide or dimethyl sulfoxide, and in the presence of a strong anhydrous base, e.g. potassium tert.-butoxide, sodium ethoxide or sodium hydride. The compound of formula Ic may be obtained by the method described and claimed in said prior specification.

The present invention further provides a process for the production of the compound of the present invention or an acid addition salt thereof, characterized in that a compound of the formula II,



II

55

in which

[Price 4s. 6d.]

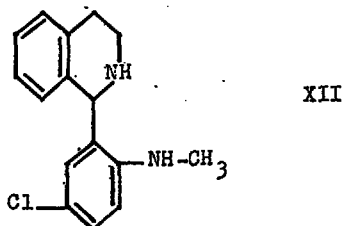
SEE ERRATA SLIP ATTACHED

A signifies either an alkyl (C_1-C_4) radical, or, if hydrolysis has taken place,

A signifies a hydrogen atom,

5 is subjected to an intramolecular ring closure and the resulting compound is then optionally converted into its acid addition salts in manner known *per se*, separation and isolation of the required (+)-isomer being effected in manner known *per se*.

10 The compound of the formula II may be produced in such a way that a compound of the formula XII



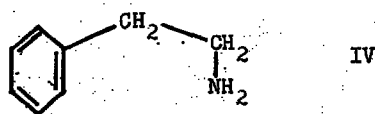
15 is heated with a chloro- or bromoacetic acid alkyl (C_1-C_4) ester in the presence of an acid binding agent.

The reaction of the compound XII with a bromoacetic acid alkyl (C_1-C_4) ester is advantageously effected in the presence of an acid binding agent (e.g. boiling the two components in an alcoholic solution of a trialkylamine for 1 to 2 hours), whereby a compound II in which A signifies a C_1-C_4 alkyl radical is obtained. This compound may be saponified to the corresponding free acid (i.e. compound II in which A=hydrogen) in manner known *per se*, e.g. by heating in an aqueous or aqueous-alcoholic solution of an alkali metal hydroxide. The ring closure of compound II (in which A=H) is advantageously effected by heating to a temperature of 120–200° C for 10 to 60 minutes. When saponification is not effected and A signifies a C_1-C_4 alkyl radical, the ring closure may be effected by boiling in the presence of Na β -methoxyethoxide in β -methoxyethanol, in tert.butanol or in isoamyl alcohol for 1 to 6 hours at 100–130° C or in glacial acetic acid at reflux.

40 The product may subsequently be isolated in manner known *per se*, e.g. by crystallization from a suitable organic solvent or by precipitation of the base as the hydrochloride from its solution in an organic solvent with gaseous hydrogen chloride and may be purified by recrystallization. The base may be obtained from its salts in manner known *per se*, e.g. by making alkaline the aqueous solution of the salt.

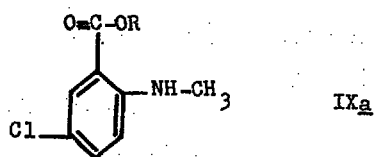
50 The starting materials of formula XII and a process for their production are described and claimed in Patent Specification No. 3328/68 (Serial No. 1,126,354); the process is as follows:—

The amine of formula IV,



55

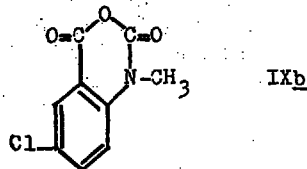
is condensed either with an *o*-amino-benzoic acid ester of formula IXa,



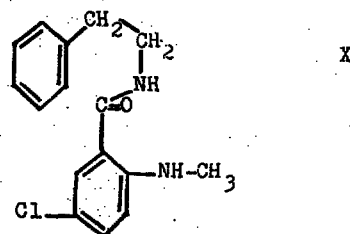
in which

R signifies an alkyl radical of from 1 to 4 carbon atoms inclusive,

(for example by heating an equimolecular mixture to 150–200° C, preferably in a vacuum, or by boiling at reflux in an inert organic solvent, e.g. dioxane, toluene or xylene), or with the isatoic acid anhydride of formula IXb,

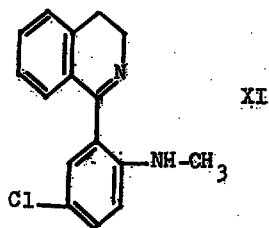


(The reaction takes place at room temperature in an inert organic solvent, e.g. tetrahydrofuran, dioxane, dimethyl formamide or dimethyl sulfoxide, with evolution of carbon dioxide; the reaction may be completed by heating in a water bath for 15 minutes). The resulting *o*-amino-benzoic acid amide of formula X,



is subjected to ring closure according to Bischler-Napieralski, e.g. by boiling in xylene in the presence of phosphorus pentoxide or in phosphorus oxychloride, to give the compound of formula XI,

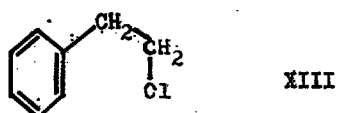
80



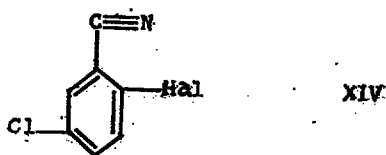
The aromatic amino radical must previously be protected, preferably by the introduction of a tosyl, benzenesulphonyl, mesyl or a similar protecting radical. These protecting radicals may be introduced in manner known *per se* by the Hinsberg reaction and are split off after the ring closure, advantageously by hydrolysis, e.g. by standing for 2 to 15 hours in concentrated sulphuric acid at room temperature.

The resulting 3,4-dihydro-isoquinoline of formula XI is preferably reduced with sodium borohydride in boiling ethanol for 1 to 3 hours or, for example, by catalytic hydrogenation in acetic acid in the presence of a platinum or nickel catalyst or by reduction using hydrogen as reducing agent, e.g. nascent hydrogen formed from zinc, tin or iron in hydrochloric acid, to give the corresponding 1,2,3,4-tetrahydro-isoquinoline of formula XII.

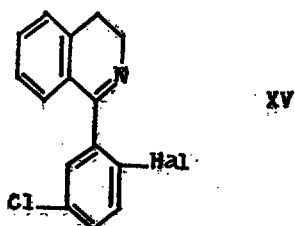
A further method for the production of compounds XII (also described and claimed in Patent Specification No. 3328/68 Serial No. 1,126,354) consists in that the compound of formula XIII,



is heated at reflux for 2 to 6 hours with a compound of formula XIV,



in which Hal signifies a chlorine or bromine atom, preferably in the presence of tin chloride or titanium tetrachloride, whereby it is advantageous to use an excess of compound XIII, and a compound of formula XV,



in which Hal has the above significance, results, which is subsequently reacted with methylamine for 2 to 12 hours at 50–60° C in the presence of copper powder and cuprous chloride, whereby the compound of formula XI results which may be reduced as described above to give the compound of formula XII.

The racemic compound of formula XII produced in accordance with the process described above may be separated into its optically active components in manner known *per se*.

(+) - 2 - chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino - [2,1 - d]benzo - [1,4]diazepin - 6 - one is a crystalline compound at room temperature; with an organic or inorganic acid it may be converted into one of its acid addition salts; examples of acids for acid addition salt formation are: fumaric, formic, acetic, citric, maleic, tartaric, methanesulphonic, salicylic, hydrochloric and sulphuric acid.

(+) - 2 - chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino - [2,1 - d]benzo - [1,4]diazepin - 6 - one and its acid addition salts are distinguished by a sedative effect on the central nervous system, whilst its toxicity is moderate or low. In pharmacological tests effected with (+)-2-chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d]benzo - [1,4]diazepin-6-one the effect on the central nervous system manifests itself in a decrease of the motor activity in mice, in an anti-convulsant effect, in potentiation action with hexobarbital, or by an amphetamine antagonism and by an inhibition of the spinal reflexes; the compounds of the invention also exhibit blood pressure lowering and inflammation inhibiting effects. Due to its sedative effect on the central nervous system (+) - 2 - chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d]benzo - [1,4]diazepin-6-one is suggested for use as a sedative, sedative/hypnotic, tranquilizer, anxiety repressor, muscle relaxant or anti-convulsant.

A suitable daily dosage for the compounds of the invention is 25 to 150 mg., calculated as the free base.

The compounds of the invention may be used as pharmaceuticals on their own or in the form of appropriate medicinal preparations for administration, e.g. orally or parenterally. In order to produce suitable medicinal preparations the compounds are worked up with organic or inorganic adjuvants which are inert and physiologically acceptable.

Examples of such adjuvants are:

- tablets and dragées : lactose, starch, talc and stearic acid;
- 5 syrups : solutions of cane sugar, invert sugar and glucose;
- 10 injectable solutions : water, alcohols, glycerin and vegetable oils.

The preparations may furthermore contain suitable preserving, stabilizing and wetting agents, solubilizers, sweetening and colouring substances and flavourings.

(+)-2-chloro-5-methyl-5,6,7,9,10,14b-hexahydro-isoquinolino-[2,1-d]benzo[1,4]diazepin-6-one may be used, for example, for oral administration in the form of a tablet having the following composition:

1—2% of binding material (e.g. tragacanth), 3—10% of starch, 2—10% of talc, 0.25—1% of magnesium stearate, the corresponding amount of active material and filling material, e.g. lactose, to make up 100%, all percentages being by weight.

The invention thus further provides pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, (+)-2-chloro-5-methyl-5,6,7,9,10,14b-hexahydro-isoquinolino-[2,1-d]benzo[1,4]-diazepin-6-one, and/or a physiologically acceptable acid addition salt thereof.

The terms "in manner known *per se*" and "known methods" as utilized herein designate methods in use or described in the literature on the subject.

In the following non-limitative Example all temperatures are indicated in degrees Centigrade and are corrected.

Example: (+)-2-chloro-5-methyl-5,6,7,9,10,14b-hexahydro-isoquinolino[2,1-d]benzo[1,4]-diazepin-6-one.

a) N-(β -phenethyl)-2-methylamino-5-chloro-benzamide.

A mixture of 2 g of 5-chloro-N-methylisatoic acid anhydride and 3 g of β -phenethylamine in 10 cc of dioxane is heated for 15 minutes in a water bath, whereby a strong carbon dioxide evolution occurs. By the addition of water to the resulting solution N-(β -phenethyl)-2-methylamino-5-chloro-benzamide, having a melting point of 129—131°, precipitates.

b) N-(β -phenethyl)-2-methyl-tosyl-amino-5-chloro-benzamide.

1 g of *p*-toluenesulphonyl chloride is added to a solution of 1 g of N-(β -phenethyl)-2-methylamino-5-chloro-benzamide in 5 cc of pyridine and the resulting mixture is heated to 60° for 1½ hours. Evaporation is then effected in a vacuum, 3 cc of acetone and 1 cc of water are added and the resulting reaction mixture is shaken for half an hour.

After evaporating the acetone, ethyl acetate is added and the organic layer is first shaken out with dilute hydrochloric acid and then with water and sodium bicarbonate solution. The organic layer is then dried over sodium sulphate and subsequently evaporated to dryness, whereby N-(β -phenethyl)-2-methyl-tosyl-amino-5-chloro-benzamide results in the form of an oily residue.

c) 1-(2-methyltosylamino-5-chlorophenyl)-3,4-dihydro-isoquinoline hydrochloride.

The crude tosylate obtained above is dissolved in 10 cc of xylene and 4 g of phosphorus pentoxide are added to the resulting solution. The resulting reaction mixture is heated for 15 hours under a reflux condenser, the xylene is subsequently evaporated in a vacuum and the viscous residue is decomposed by the addition of ice. The aqueous mixture is made alkaline with a concentrated aqueous sodium hydroxide solution and subsequently extracted with methylene chloride. After drying and removing the organic solvent the oily residue is dissolved in diethyl ether and dry hydrogen chloride gas is introduced, whereby 1-(2-methyltosylamino-5-chlorophenyl)-3,4-dihydro-isoquinoline hydrochloride, having a melting point of 240—241°, precipitates.

d) 1-(2-methylamino-5-chlorophenyl)-3,4-dihydro-isoquinoline.

4 g of concentrated sulphuric acid are gradually added whilst cooling to 1 g of 1-(2-methyltosylamino-5-chlorophenyl)-3,4-dihydro-isoquinoline hydrochloride and the resulting solution is left to stand overnight at room temperature. The solution is then poured on ice, made alkaline with sodium hydroxide and the alkaline solution is extracted with methylene chloride. After drying the organic solvent is evaporated, whereby 1-(2-methylamino-5-chlorophenyl)-3,4-dihydro-isoquinoline is obtained as an oily residue.

e) 1-(2-methylamino-5-chlorophenyl)-1,2,3,4-tetrahydro-isoquinoline.

A solution of 1 g of crude 1-(2-methylamino-5-chlorophenyl)-3,4-dihydro-isoquinoline in 8 cc of acetic acid is hydro-

generated in an atmosphere of hydrogen at room temperature and normal pressure after the addition of 0.05 g of platinum catalyst. The catalyst is then filtered off, the filtrate is evaporated in a vacuum, the residue is dissolved in methylene chloride and this solution is shaken with dilute aqueous sodium hydroxide solution. After drying and evaporating the organic layer pentane is added, whereby 1 - (2 - methylamino - 5-chloro - phenyl) - 1,2,3,4 - tetrahydro - isoquinoline crystallizes in the form of white prisms having a melting point of 141—143°; this material is racemic.

f) Separation of the racemic 1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4-tetrahydro-isoquinoline into its optical antipodes.

A solution of 15 g of ($\pm$)-1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline in 200 cc of ethanol and 100 cc of methylene chloride are added to a solution of 8.25 g of d-tartaric acid in 100 cc of ethanol. On concentrating this mixture only the tartrate of the (+) base precipitates. The precipitate is filtered off and the base is liberated from its salt by shaking the salt with methylene chloride and a dilute aqueous sodium hydroxide solution. The organic phase is dried and the solvent is removed in a vacuum. By recrystallizing the resulting crude base from ethanol (+)-1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline, $[\alpha]_{546}^{20} = +27.3^\circ$ (c=2 in ethanol), is obtained. The filtrate from the tartrate of the (+) base is evaporated to dryness in a vacuum and the residue is shaken with methylene chloride and a dilute aqueous sodium hydroxide solution. Subsequently the organic phase is dried and the solvent is removed in a vacuum. The residue, mainly consisting of the (-) base, is converted into the d-tartrate by the addition of d-tartaric acid in a manner analogous to that described above. The (-) - 1 - (2 - methylamino - 5 - chloro-phenyl) - 1,2,3,4 - tetrahydro - isoquinoline base, liberated from its tartrate in a manner analogous to the (+) base, has $[\alpha]_{546}^{20} = -27.8^\circ$ (c=2 in ethanol).

g) (-) - 1 - (2 - methylamino - 5 - chloro-phenyl) - 2 - carbethoxymethyl - 1,2,3,4-tetrahydro-isoquinoline.

A mixture of 6 g of (-)-1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline, 8 g of ethylbromo-acetate and 4 g of triethylamine in 34 cc of ethanol is heated for 90 minutes under a reflux condenser. The resulting light yellow solution is subsequently cooled to 60° and 14 cc of water are slowly added during the course of 15

minutes, whereby coarse crystals precipitate. The crystals are filtered and washed with water. (-) - 1 - (2 - methylamino - 5-chloro - phenyl) - 2 - carbethoxymethyl - 1,2,3,4-tetrahydro-isoquinoline, having a melting point of 104—106°, is obtained in the form of white prisms.

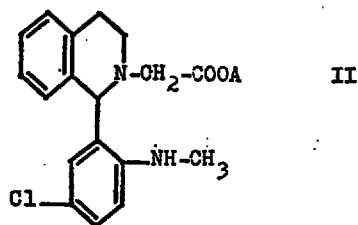
h) (+) - 2 - chloro - 5 - methyl-5,6,7,9,10,14b - hexahydro - isoquinolino-[2,1 - d]benzo[1,4]diazepin - 6 - one.

1 g of (-)-1-(2-methylamino-5-chloro-phenyl) - 2 - carbethoxymethyl - 1,2,3,4-tetrahydro-isoquinoline is heated to the boil in glacial acetic acid and the organic solvent is distilled off at atmospheric pressure for $\frac{1}{2}$ to 3 hours. After removing the remaining portions of volatile solvent in a vacuum ethanol is added, whereby (+)-2-chloro-5-methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d]benzo[1,4]diazepin - 6-one, having a melting point of 190—195°, crystallizes.

WHAT WE CLAIM IS:—

1. (+) - 2 - chloro - 5 - methyl-5,6,7,9,10,14b - hexahydro - isoquinolino-[2,1 - d]benzo - [1,4]diazepin - 6 - one and its acid addition salts.

2. A process for the production of a compound as claimed in Claim 1, which comprises subjecting to intramolecular ring closure a racemate or optically active form corresponding to the required product of the formula II



wherein A is an alkyl (C_1-C_4) radical or hydrogen atom

and, when an acid addition salt is required, the resulting compound is reacted with an organic or inorganic acid, separation and, if necessary, isolation of the required (+)-isomer being effected in manner known *per se*.

3. A process according to Claim 2, in which the compound of the formula II is produced by heating a racemate or optically active form corresponding to the required product of the formula XII

genated in an atmosphere of hydrogen at room temperature and normal pressure after the addition of 0.05 g of platinum catalyst. The catalyst is then filtered off, the filtrate is evaporated in a vacuum, the residue is dissolved in methylene chloride and this solution is shaken with dilute aqueous sodium hydroxide solution. After drying and evaporating the organic layer pentane is added, whereby 1 - (2 - methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro - isoquinoline crystallizes in the form of white prisms having a melting point of 141—143°; this material is racemic.

f) Separation of the racemic 1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline into its optical antipodes.

A solution of 15 g of (±)-1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline in 200 cc of ethanol and 100 cc of methylene chloride are added to a solution of 8.25 g of d-tartaric acid in 100 cc of ethanol. On concentrating this mixture only the tartrate of the (+) base precipitates. The precipitate is filtered off and the base is liberated from its salt by shaking the salt with methylene chloride and a dilute aqueous sodium hydroxide solution. The organic phase is dried and the solvent is removed in a vacuum. By recrystallizing the resulting crude base from ethanol (+)-1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline, $[\alpha]_{546}^{20} = +27.3^\circ$ (c=2

in ethanol), is obtained. The filtrate from the tartrate of the (+) base is evaporated to dryness in a vacuum and the residue is shaken with methylene chloride and a dilute aqueous sodium hydroxide solution. Subsequently the organic phase is dried and the solvent is removed in a vacuum. The residue, mainly consisting of the (-) base, is converted into the d-tartrate by the addition of d-tartaric acid in a manner analogous to that described above. The (-) - 1 - (2 - methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro - isoquinoline base, liberated from its tartrate in a manner analogous to the (+) base, has $[\alpha]_{546}^{20} = -27.8^\circ$ (c=2 in ethanol).

g) (-) - 1 - (2 - methylamino - 5 - chloro - phenyl) - 2 - carbethoxymethyl - 1,2,3,4 - tetrahydro-isoquinoline.

A mixture of 6 g of (-)-1-(2-methylamino - 5 - chloro - phenyl) - 1,2,3,4 - tetrahydro-isoquinoline, 8 g of ethylbromo-acetate and 4 g of triethylamine in 34 cc of ethanol is heated for 90 minutes under a reflux condenser. The resulting light yellow solution is subsequently cooled to 60° and 14 cc of water are slowly added during the course of 15

minutes, whereby coarse crystals precipitate. The crystals are filtered and washed with water. (-) - 1 - (2 - methylamino - 5 - chloro - phenyl) - 2 - carbethoxymethyl - 1,2,3,4-tetrahydro-isoquinoline, having a melting point of 104—106°, is obtained in the form of white prisms.

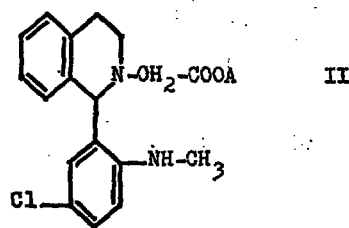
h) (+) - 2 - chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino [2,1 - d]benzo[1,4]diazepin - 6 - one.

1 g of (-)-1-(2-methylamino-5-chloro-phenyl) - 2 - carbethoxymethyl - 1,2,3,4-tetrahydro-isoquinoline is heated to the boil in glacial acetic acid and the organic solvent is distilled off at atmospheric pressure for $\frac{1}{2}$ to 3 hours. After removing the remaining portions of volatile solvent in a vacuum ethanol is added, whereby (+)-2-chloro-5-methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d]benzo[1,4]diazepin - 6-one, having a melting point of 190—195°, crystallizes.

WHAT WE CLAIM IS:—

1. (+) - 2 - chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino [2,1 - d]benzo - [1,4]diazepin - 6 - one and its acid addition salts.

2. A process for the production of a compound as claimed in Claim 1, which comprises subjecting to intramolecular ring closure a racemate or optically active form corresponding to the required product of the formula II

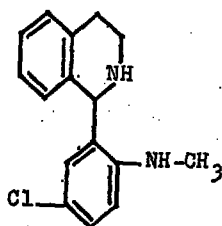


wherein A is an alkyl (C₁—C₄) radical or hydrogen atom

and, when an acid addition salt is required, the resulting compound is reacted with an organic or inorganic acid, separation and, if necessary, isolation of the required (+)-isomer being effected in manner known *per se*.

3. A process according to Claim 2, in which the compound of the formula II is produced by heating a racemate or optically active form corresponding to the required product of the formula XII





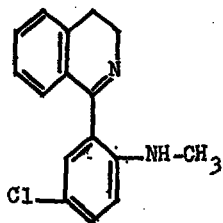
XII

with a chloro- or bromoacetic acid alkyl (C₁-C₄) ester in the presence of an acid binding agent and, when A in compound II is to signify a hydrogen atom, effecting hydrolysis.

5

4. A process according to Claim 3, in which the compound of formula XII set forth in Claim 3 is produced by reducing the compound of the formula XI

10

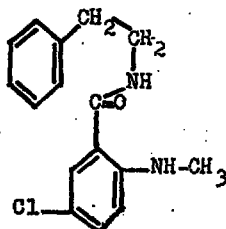


XI

and optionally effecting optical resolution to obtain the (-)-isomer.

15

5. A process according to Claim 4, in which the compound of the formula XI set forth in Claim 4 is produced by subjecting the compound of the formula X

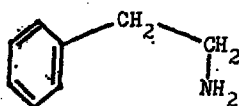


X

20 to a ring closure according to BISCHLER-NAPIERALSKI, the amino radical being protected prior to ring closure and the protecting radical being split off after ring closure.

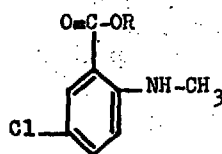
6. A process according to Claim 5, in which the compound of the formula X set forth in Claim 5 is produced by condensing the compound of the formula IV

25



IV

with a compound of the formula IXa



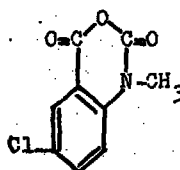
IXa

30

wherein R is an alkyl radical of from 1 to 4 carbon atoms.

7. A process according to Claim 5, in which the compound of the formula X set forth in Claim 5 is produced by condensing the compound of the formula IV set forth in Claim 6 with the compound of the formula IXb

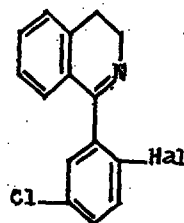
35



IXb

8. A process according to Claim 4, in which the compound of the formula XI set forth in Claim 4 is produced by reacting a compound of the formula XV

40



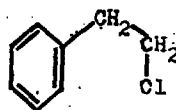
XV

wherein Hal is a chlorine or bromine atom with methylamine for 2 to 12 hours at 50 to 60° C in the presence of copper powder and cuprous chloride.

45

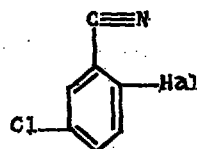
9. A process according to Claim 8, in which the compound of the formula XV set forth in Claim 8 is produced by heating the compound of the formula XIII

50



XIII

with a compound of the formula XIV



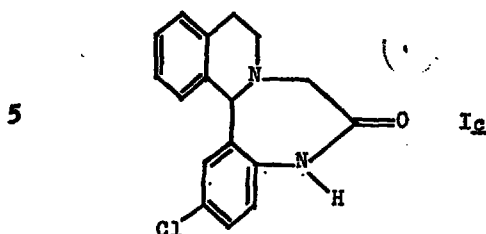
XIV

55

wherein Hal has the meaning set forth in Claim 8.



10. A process for the production of a compound as claimed in Claim 1, which comprises heating the compound of the formula Ic



with methyl chloride, methyl bromide or methyl iodide in an inert solvent and in the presence of a base, and, when an acid addition salt is required, reacting with an organic or inorganic acid, separation and isolation of the required (+)-isomer being effected in manner known *per se*.

11. A process for the production of (+)-2-chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d] - benzo - [1,4] - diazepin-6-one and its acid addition salts substantially as herein described with reference to the Example.

12. A compound as claimed in Claim 1 whenever produced by the process claimed in any one of Claims 2 to 11.

13. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, (+) - 2 - chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d]benzo[1,4] - diazepin - 6 - one, and/or a physiologically acceptable acid addition salt thereof.

14. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, an amount of (+)-2-chloro-5-methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d]benzo[1,4]diazepin - 6-one suitable for the administration of a daily dosage of 25 to 150 mg.

15. Pharmaceutical compositions containing 1 to 2% of binding material, 3 to 10% of starch, 2 to 10% of talc, 0.25 to 1% of magnesium stearate, an amount of (+)-2-chloro - 5 - methyl - 5,6,7,9,10,14b - hexahydro - isoquinolino[2,1 - d] - benzo[1,4] - diazepin-6-one suitable for the administration of a daily dosage of from 25 to 150 mg and filling material to make up 100%, the percentages being by weight.

For the Applicants,
G. H. MUNSTER & CO.,
Chartered Patent Agents,
Imperial Buildings, 56, Kingsway,
London, W.C.2.

