

1017,276



PATENT SPECIFICATION

NO DRAWINGS

1017,276

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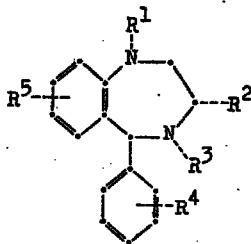
COMPLETE SPECIFICATION

Novel 1,4-Benzodiazepine Derivatives

We, F. HOFFMANN-LA ROCHE & Co., Aktien-
gesellschaft, a Swiss Company of 124—184
Grenzacherstrasse, Basle, Switzerland, do
hereby declare the invention, for which we
5 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 novel 1,4-benzo-
10 diazepine derivatives; more particularly, it
relates to 5 - phenyl - 1,2 - dihydro - 3H -
1,4-benzodiazepines and 5-phenyl-1,2,4,5-
tetrahydro-3H-1,4-benzodiazepines.

The 1,2,4,5-tetrahydro derivatives are com-
15 pounds of the formula



(I)

wherein R¹ and R³ represent lower alkyl, lower
alkenyl or lower alkanoyl groups, R² repre-
20 sents a lower alkyl group, R⁴ and R⁵ repre-
sent halogen atoms or trifluoro-methyl, nitro,
amino, lower alkanoylamino, lower alkylthio,
lower alkoxy, lower alkyl, cyano, carboxy,
lower alkoxy-carbonyl or di(lower alkyl)-amino
25 groups and the broken lines denote that the
R-substituents attached thereby are optional,

[Price 4s. 6d.]

and acid addition salts of the basic compounds.
The 1,2-dihydro derivatives of the invention
are 4,5-dehydro-derivatives of the formulated
compounds in which R³ is absent and of their
30 salts.

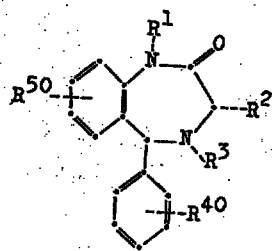
The term 'lower' is used in this description
and in the accompanying claims to mean that
the groups qualified thereby contain not more
than seven carbon atoms. Thus, the term
35 'lower alkyl' means straight or branched
chain C₁—C₇ alkyl groups such as
methyl, ethyl, propyl, isopropyl or butyl.
Again the term 'lower alkenyl' means
straight and branched chain C₂—C₇
40 alkenyl groups in which there is at
least one double bond, such as allyl.
Further, the term 'lower alkanoyl' means acyl
groups derived from C₁—C₇ alkanolic acids
such as acetyl or propionyl. Still further, the
45 term 'lower alkoxy-carbonyl' means alkoxy-
carbonyl groups containing from two to seven
carbon atoms. Preferred substances of the in-
vention are those in which one or both of
the substituents R⁴ and R⁵ are present and
50 represent halogen atoms or trifluoro-methyl,
nitro, lower alkylthio, cyano, amino and di
(lower alkyl)-amino groups. Especially pre-
ferred are those substances bearing a sub-
stituent in the 7 and/or 2¹-positions, especially
55 a halogen, trifluoro-methyl or amino sub-
stituent. The most preferred substances are
the 4,5-dehydro derivatives of the compounds
of formula I in which R³ is absent, R¹ is
present and represents a lower-alkyl group,
60 R² and R⁴ are absent and R⁵ is present in
the 7-position and represents a halogen atom
or an amino group.

The basic compounds form acid addition
salts. Suitable acid addition salts are those
with pharmaceutically acceptable inorganic 65

and organic acids such as nitric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, acetic acid, citric acid, succinic acid, benzoic acid, formic acid or *p*-toluene-sulphonic acid.

The novel compounds aforesaid are manufactured, also in accordance with the invention, in various ways. Certain of these ways are only applicable in certain cases where the substituents are appropriate. The substituents which may be present in any particular case are mentioned in the description of the particular reaction involved.

Thus, one embodiment of the process of the invention comprises reacting a compound of the general formula



(II)

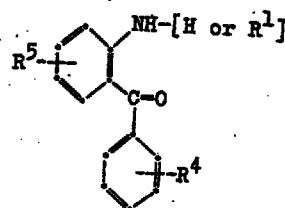
wherein R¹, R², R³ and the broken lines have the significance already given and R⁴⁰ and R⁵⁰ represent halogen atoms or trifluoromethyl, amino, nitro, lower alkylthio, lower alkoxy, lower alkyl or di(lower alkyl)-amino groups, or a 4,5-dehydro derivative thereof in which R³ is absent, with lithium aluminium hydride.

This reaction can be performed at room temperature as well as above or below room temperature. The reaction is preferably carried out in an inert organic solvent, such as tetrahydro-furan, benzene, dioxane or diethyl ether. The reaction is effected under anhydrous conditions. Treatment of the 4,5-dehydro derivatives of the compounds of formula II with lithium aluminium hydride has been found to yield 5-phenyl-1,2-dihydro-3H-1,4-benzodiazepines as well as 5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepines. It has been found that the application of heat favours the formation of the 1,2,4,5-tetrahydro compounds, as also does the presence of a substituent in the 1-position. Treatment of compounds of formula II wherein R³ is absent or is a lower alkyl, lower alkenyl or lower alkanoyl group yields, of course, a

1,2,4,5-tetrahydro derivative. In cases where a 1,2-dihydro compound is formed, further treatment with a suitable reducing agent will result in the production of the 1,2,4,5-tetrahydro derivative.

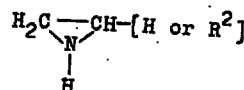
Where compounds in which one or more of the substituents R², R⁴⁰ and R⁵⁰ is susceptible to reduction by lithium aluminium hydride are used, such a substituent will, of course, be reduced. For example, if R⁴⁰ or R⁵⁰ is present and is nitro, it will be reduced to amino. Also, when R¹ or R² is present and is lower alkanoyl, reduction to lower alkyl results.

A second embodiment of the process of the invention comprises reacting a compound of the general formula



(III)

wherein R¹, R⁴, R⁵ and the broken lines have the significance given earlier, with a compound of the general formula

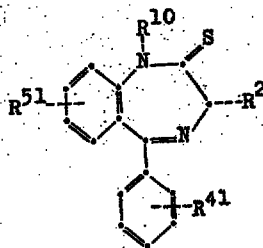


(IV)

wherein R² has the significance given earlier.

The foregoing reaction can be conducted at room temperature or above or below room temperature, but it is preferably effected with the application of heat. Temperatures of from about 20°C to about 100°C are preferred. Further, the reaction is preferably conducted in the presence of an inert organic solvent such as tetrahydro-furan, benzene, dioxane or diethyl ether.

Still another embodiment of the process of the invention comprises treating a compound of the general formula

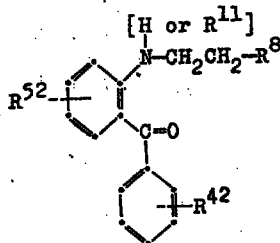


(V)

wherein R^2 and the broken lines have the significance given earlier, R^{10} represents lower alkyl or lower alkenyl, R^{41} and R^{51} represent halogen atoms or trifluoro-methyl, amino, lower alkanoylamino, lower alkoxy, lower alkyl, cyano, carboxy, lower alkoxy-carbonyl or di(lower alkyl)-amino groups, with RANEY-nickel in the presence of a suitable solvent.

The treatment can be effected at room temperature or below or with the application of heat. It is preferably effected by heating the reaction mixture under reflux. The treatment can preferably be conducted in an inert organic solvent such as acetone, ethanol, dioxane or tetrahydro-furan. It should be borne in mind that where the R^{41} and/or R^{51} substitution is halogen, such substitution may be removed during the treatment.

Yet another embodiment of the process of the invention comprises hydrolysing and cyclising a compound of the general formula



(VI)

wherein R^{11} represents a lower alkyl or lower alkenyl or tosyl group and R^{42} and R^{52} represent halogen atoms or lower alkanoylamino, trifluoro-methyl, nitro, lower alkylthio, lower alkoxy, lower alkyl, carboxy, lower alkoxy-carbonyl, cyano or di(lower alkyl)-amino groups and the broken lines have the same meaning as hitherto and R^8 is an acylamino group, either by treatment with an alkaline agent or by treatment with an acid followed by treatment with a basic agent.

The hydrolysis is preferably conducted in acid media. One preferred embodiment involves the use of strong mineral acids such as sulphuric acid or hydrochloric acid. The hydrolysis reaction can be conducted at room temperature or elevated temperatures, and is preferably conducted with the application of heat. When starting materials contain substituents susceptible to acid hydrolysis the substituents are hydrolysed during the hydrolysis step. For example, when the hydrolysis is carried out under strong alkaline or strong acid conditions, any trifluoromethyl substituent present will be hydrolysed to carboxy. Again, for example, lower alkoxy-carbonyl and cyano substituents both hydrolyse to carboxy and lower alkanoylamino hydrolyses to amino.

The product of an acid hydrolysis is an acid addition salt of a 2-aminoethylamino-benzophenone and this can be cyclised by treatment with a basic agent (e.g. an alkali or pyridine). In the case where an alkaline agent is used for the hydrolysis, the cyclisation product is, of course, directly obtained.

Certain products of the process (i.e. compounds of formula I or their 4,5-dehydro derivatives in which R^3 is absent) can be converted to other products still falling within the scope of the invention. For example, products wherein either R^1 or R^3 is absent can be converted into products wherein R^1 or R^3 is present and is a lower alkyl, lower alkenyl or lower alkanoyl group by alkylation or alkenylation or alkanoylation as the case may be. The 1,2,4,5-tetrahydro compounds can be obtained by reduction of the corresponding 1,2-dihydro compounds. Products wherein R^1 (R^{50} , R^{51} or R^{52}) is absent can be nitrated. Products wherein R^4 (R^{40} or R^{41}) or R^5 (R^{50} or R^{51}) is an amino group can be lower-alkanoylated to yield corresponding products bearing a lower alkanoylamino substituent, or can be reacted to effect replacement of the amino group by a cyano or halogen substituent. Furthermore, products wherein R^4 (R^{40} or R^{41}) or R^5 (R^{50} or R^{51}) is a nitro group can be reduced to the corresponding amino-substituted product. Again, any trifluoromethyl-substituted product can be converted into a carboxy-substituted product or methoxycarbonyl-substituted product by hydrolysis with a strong acid and cyclisation by treatment with a base and, where the methoxycarbonyl-substituted product is required, by methylation of the cyclisation product.

Those starting compounds of formula II hereinbefore in which R^1 (when present) represents a lower alkyl or lower alkenyl group, R^3 is absent, R^{40} (when present) represents a halogen atom or a trifluoro-methyl, lower alkoxy or lower alkyl group and R^{50} (when present) represents a halogen atom or a trifluoro-methyl, amino, nitro, lower alkylthio, lower alkoxy or lower alkyl group, and their

4,5-dehydro derivatives, are claimed *per se* in the specification of our Letters Patent No. 972,968.

5 Those starting compounds of formula III hereinbefore in which R¹ is present as a lower alkenyl group, R⁴ is absent and R⁵ is present as a halogen atom in the 5-position are claimed *per se* in the specification of our Letters Patent No. 972,971.

10 Those starting compounds of formula III hereinbefore in which R¹ and R⁴ are absent and R⁵ is present as a lower alkylthio group in the 5-position are claimed *per se* in the specification of our Letters Patent No. 972,972.

15 Those starting compounds of formula III hereinbefore in which R¹ is absent, R⁴ (when present) is a trifluoro-methyl group in the 2¹-position and R⁵ is a trifluoro-methyl group in the 5-position are claimed *per se* in the specification of our Letters Patent No. 972,973.

20 The starting compound of formula III hereinbefore in which R¹ is present as the methyl group, R⁴ is absent and R⁵ is present as a chlorine atom in the 5-position is claimed *per se* in the specification of our Letters Patent No. 972,975.

25 Those starting compounds of formula III hereinbefore in which R¹ is absent, at least one of R⁴ and R⁵ is present and is a carboxy, lower alkoxycarbonyl or cyano group and the other (when present) is such a group or a lower alkyl, lower alkoxy, lower alkylthio, nitro or trifluoro-methyl group (R⁵ being in the 5-position when present) are claimed *per se* in the specification of our copending application for Letters Patent No. 12819/64 (now serial no: 985,658).

30 The starting compounds of formula V hereinbefore in which R¹⁰ (when present) is a lower-alkyl group and R⁴¹ (when present) and R⁵¹ (when present) represent halogen atoms or trifluoro-methyl, lower-alkoxy, lower-alkyl or di(lower alkyl)-amino groups are claimed *per se* in the specification of our copending application for Letters Patent No. 37643/64 (now serial no: 1,016,668).

35 The compounds of formula VI hereinbefore in which R¹¹ represents a lower-alkyl group, R⁸ represents the benzamido or phthalimido group, R⁴² (when present) is a halogen atom or the trifluoro-methyl group and R⁵² (when present) is a halogen atom or the trifluoro-methyl or nitro group are claimed in the specification of our copending application for Letters Patent No. 37642/64 (now serial no: 1,016,667).

40 The preferred starting compounds for the process of the present invention are those in which one or both of the substituents R⁴ (R⁴⁰, R⁴¹ or R⁴²) and R⁵ (R⁵⁰, R⁵¹ or R⁵²) are halogen atoms or trifluoro-methyl, nitro (except in the case of treatment of a compound of formula V), lower-alkylthio (except in the

case of treatment of a compound of formula V), cyano (except in the case of the reaction of a compound of formula I with lithium aluminium hydride), amino (except in the case of hydrolysis of a compound of formula VI) or di(lower alkyl)-amino. Especially preferred starting compounds are those which contain a substituent in the 7- (or 5-) and/or 2¹-position.

Compounds of formula I and their 4,5-dehydro derivatives in which R³ is absent and medicinally acceptable acid-addition salts of such compounds are valuable therapeutic agents being useful as muscle relaxants, sedatives and anticonvulsants. They may be used as medicaments in the form of pharmaceutical preparations which contain one or more of the compounds or salts in admixture with a compatible pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed compatible substances such as water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly or any other known carrier useful in the preparation of medicaments. The pharmaceutical preparations may be in solid form, for examples as tablets, dragees, suppositories or capsules, or in liquid form, for example, as solutions, emulsions or suspensions. 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 following examples are illustrative of the ways in which the novel heterocyclic compounds of the invention may be made:

EXAMPLE 1.

A) The preparation of the starting material:

The 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) starting material was prepared as described in the specification of our Letters Patent No. 972,967.

B) The process

To a mixture of 6 g of lithium aluminium hydride and 100 ml of dry tetrahydro-furan was added in small portions with stirring a solution of 21.6 g of 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) in 300 ml of dry tetrahydro-furan. The mixture was heated under reflux until it darkened. This took about 10 minutes. It was then cooled to ca 20°C and stirred for an additional 0.5 hour. The excess lithium aluminium hydride was decomposed with ethyl acetate and wet ether. The mixture was filtered over diatomaceous earth, the organic layer was separated, dried and concentrated *in vacuo*. The residue was crystallized from ether and yielded 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine which, on recrystallization

from petroleum ether (boiling point = 30°—60°C), formed yellow needles melting at 170°—171°C.

- 5 To a solution of 10.2 g of the foregoing benzodiazepine in 100 ml of N,N-dimethylformamide were added with stirring 2 g of a 53% mineral oil dispersion of sodium hydride. The mixture was heated in a water bath at 65°C for 35 minutes and cooled to ca 20°C.
- 10 Then, 3.6 ml of methyl iodide were added thereto. After stirring for 0.5 hour, the reaction mixture was poured into ice-water and extracted with methylene chloride. The organic layer was separated, dried and concentrated
- 15 in *vacuo* to dryness. The residue was dissolved in a small amount of a mixture of ether and petroleum ether (1:1) and adsorbed on a chromatographic column (3.5 cm. diameter) prepared with 300 g of WOELM alumina (grade I) and the same solvent mixture. The column was eluted first with 2.8 l of an ether/(petroleum ether) mixture (1:1), then with 500 ml of a 75% ether/(petroleum ether) mixture (3:1), followed by 500 ml of absolute ether. The eluates were combined and concentrated in *vacuo*. The residue was crystallized from a small amount of a mixture of ether and petroleum ether yielding
- 20 crude 7-chloro-5-phenyl-1-methyl-1,2-dihydro-3H-1,4-benzodiazepine.

EXAMPLE 2.

- To a cooled, stirred suspension of 8.9 g of anhydrous aluminium chloride in 100 ml of dry benzene were added 20 g of 2-amino-5-chloro-benzophenone. The reaction mixture was heated to reflux temperature. Then the heating was stopped and a solution of 1.9 g of ethyleneimine in 25 ml of benzene was added in small portions. The reaction mixture was stirred for about 0.5 hour and poured on to ice. After the addition of 30 g of potassium hydroxide, the organic layer was separated and washed with 2-N hydrochloric acid.

- 45 The aqueous acidic layer was made alkaline with dilute alkali and extracted with ether. The ether layer was dried and concentrated in *vacuo*. The residue was crystallized from ether and yielded 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine.

- 50 A solution of 1 g of the foregoing benzodiazepine in a mixture of 15 ml of pyridine and 10 ml of acetic anhydride was left at ca 20°C for 5 hours and then concentrated in *vacuo* to dryness. The residue was crystallized from ether and yielded 1-acetyl-7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine which, on recrystallization from a mixture of methylene chloride, ether and petroleum ether, formed colourless prisms melting at 165°—166°C.

EXAMPLE 3.

- 60 A) *The preparation of the starting material.*
The 7-chloro-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) starting

material was prepared as described in the specification of our Letters Patent No. 972,968. 65

B) *The process*

- To 6.9 g of lithium aluminium hydride in 150 ml of dry tetrahydro-furan was added a solution of 21 g of 7-chloro-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) in 300 ml of tetrahydro-furan. The addition was carried out as fast as the foaming permitted. Then the mixture was heated to reflux and the violent reaction moderated by cooling. The mixture was then stirred at ca 20°C until the reaction had subsided, then heated under reflux for 0.5 hour, decomposed with ethyl acetate and wet ether and filtered over diatomaceous earth. The organic layer was separated, dried and concentrated in *vacuo* to dryness. The oily residue was dissolved in methanol and acidified with a slight excess of methanolic hydrogen chloride. Acetone was added causing the crystallization of the crude 7-chloro-5-phenyl-1,2,4,5-tetrahydro-3H-benzodiazepine hydrochloride which was filtered off. A further sample was crystallized from a mixture of methanol and acetone and formed slightly yellow plates of 7-chloro-5-phenyl-1,2,4,5-tetrahydro-3H-benzodiazepine hydrochloride melting at 259°—260°C with decomposition. 70 75 80 85 90

EXAMPLE 4

- A) *The preparation of the starting material* 95

The 5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) starting material was prepared as described in the specification of our Letters Patent No. 972,968.

B) *The process:*

- To 1.5 g of lithium aluminium hydride in 100 ml of anhydrous ether were added 4.7 g of 5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2). The reaction mixture was stirred at ca 20°C for 1 hour, heated under reflux for 5 hours and then cooled. Wet ether was added and the mixture was filtered over diatomaceous earth. The filtrate was dried and concentrated in *vacuo* to dryness. The oily residue was crystallized from a mixture of ether and petroleum ether yielding 5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine which, on crystallization from petroleum ether, formed yellow needles melting at 145°—147°C. 100 105 110

EXAMPLE 5

- A) *The preparation of the starting material.* 115

The 7-chloro-5-(2-chloro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) starting material was prepared as described in the specification of our Letters Patent No. 972,968. 120

B) *The process.*

- 9.5 g of 7-chloro-5-(2-chloro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) contained in a SOXHLET extractor was slowly eluted by extraction with ether which 125

was being heated under reflux, into a boiling solution 2.5 g of lithium aluminium hydride in 500 ml of absolute ether. After 22 hours all starting material had dissolved and a yellow precipitate formed. The excess lithium aluminium hydride was destroyed by the cautious addition of 10 ml of water, the resulting mixture was dried with a large amount of sodium sulphate and filtered. The ether solution, on concentration and addition of petroleum ether, yielded yellow crystals of 7-chloro-5-(2-chloro-phenyl) - 1,2 - dihydro - 3H - 1,4 - benzo-diazepine which, after recrystallization from a mixture of benzene and petroleum ether, melted at 175°—177°C.

EXAMPLE 6

A) The preparation of the starting material

The 1 - methyl - 7 - chloro - 5 - (2 - chloro-phenyl) - 2,3 - dihydro - 1H - 1,4 - benzo-diazepinone-(2) starting material was prepared as described in the specification of our Letters Patent No. 972,968.

B) The process

10 g of 7-chloro-5-(2-chloro-phenyl)-1-methyl - 2,3 - dihydro - 1H - 1,4 - benzo-diazepinone-(2) contained in a SOXHLET extractor were slowly eluted by extraction with ether which was being heated under reflux into a boiling solution containing 2.5 g of lithium aluminium hydride in 500 ml of absolute ether. After 18 hours all starting material was dissolved and a pink solution formed. The excess lithium aluminium hydride was destroyed by the cautious addition of a small amount of water and the resulting mixture was dried with sodium sulphate and filtered. The ether solution, on concentration and addition of petroleum ether, yielded colourless prisms of 7-chloro-5-(2-chloro-phenyl) - 1 - methyl - 1,2,4,5 - tetrahydro - 3H-1,4-benzodiazepine which, after recrystallization from a mixture of benzene and petroleum ether, melted at 133°—135°C.

EXAMPLE 7

A) The preparation of the starting material

11.5 g of 7-chloro-5-(2-chloro-phenyl)-1-methyl - 2,3 - dihydro - 1H - 1,4 - benzo-diazepinone - (2) were dissolved in 200 ml of acetic acid and, after the addition of 0.5 g of platinum oxide, shaken in a hydrogen atmosphere (1 atmosphere, 25°C). After the uptake of 1050 ml of hydrogen, the catalyst was filtered off, the solvent evaporated, the residue treated with a sodium hydroxide solution and filtered. Crystals of 7-chloro-5-(2-chloro - phenyl) - 1 - methyl - 1,2,4,5 - tetrahydro-1H-1,4-benzodiazepinone-(2) were obtained and after several recrystallizations from alcohol and ether melted at 168°—171°C.

B) The process

5 g of 7-chloro-5-(2-chloro-phenyl)-1-methyl - 1,2,4,5 - tetrahydro - 3H - 1,4-benzodiazepinone-(2) contained in a SOXHLET ex-

tractor was slowly eluted, by extracting with ether which was being heated under reflux, into a boiling solution of 1.19 g of lithium aluminium hydride in 350 ml of ether. After heating under reflux for 22 hours, the excess lithium aluminium hydride was destroyed by the addition of 10 ml of water. The emulsion was dried with sodium sulphate, filtered and concentrated. The residue was crystallized by the addition of petroleum ether and the product then recrystallized from a mixture of benzene and petroleum ether to form prisms of 7 - chloro - 5 - (2 - chloro - phenyl) - 1 - methyl - 1,2,4,5 - tetrahydro - 3H - 1,4-benzodiazepine melting at 133°—135°C.

EXAMPLE 8

A) The preparation of the starting material

The 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone-(2) starting material was prepared as described in the specification of our Letters Patent No. 972,964.

B) The process

A solution of 57.0 g of 7-chloro-1-methyl-5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzo-diazepinone-(2) in 500 ml of anhydrous tetrahydro-furan (distilled over lithium aluminium hydride and freshly filtered through activated alumina) was added dropwise over 2 hours to a stirred suspension (heated under reflux) of 15.2 g of lithium aluminium hydride in 500 ml of anhydrous tetrahydro-furan. After the addition was complete, stirring and heating under reflux were continued for a further 3 hours and the mixture was then cooled in an ice-bath and treated dropwise with excess saturated aqueous sodium sulphate solution, followed by anhydrous sodium sulphate to dry the products. The inorganic salts were filtered off, washed thoroughly with ether and the filtrates were evaporated to yield the crude product as a gum. This was dissolved in ether and the basic material was extracted into ice-cold 1-N hydrochloric acid. The acid extract was cooled with ice and basified with 3-N sodium hydroxide solution, resulting in precipitation of the products. The precipitate was extracted into ether, the extract was washed with water, dried over magnesium sulphate and evaporated, yielding 7-chloro-1-methyl - 5 - phenyl - 1,2,4,5 - tetrahydro - 3H-1,4-benzodiazepine as a pale brown gum. This material was converted to the hydrochloride by the addition of 2-N hydrochloric acid in 1.05 equivalents of methanol followed by ether and petroleum ether to precipitate the hydrochloride. The latter was further purified by washing with benzene and upon recrystallization from methanol/ether/(petroleum ether) it formed pale yellow plates. This material was converted to the free base by treatment with ice-cold dilute sodium hydroxide solution and extraction with ether. Evaporation of the ether extract yielded a

5 pale yellow gum which was readily crystallized from pentane at -70°C . Further recrystallizations from pentane yielded pale yellow needles of 7-chloro-1-methyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine melting at 60° — 62°C .

10 The base was reconverted into the hydrochloride by treatment with methanolic hydrochloric acid, followed by the addition of ether and petroleum ether as previously. After further recrystallizations from methanol/ether it formed colourless needles of melting point 258° — 259°C .

15 The base was also converted to the monopicrate by treatment of a solution of the base in ether with an ethereal solution of 1 equivalent of picric acid. The resulting crystalline picrate was further recrystallized from acetone/hexane and then from ethanol, yielding bright yellow prisms of melting point 202° — 204°C .

20 2.00 g of 7-chloro-1-methyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine were dissolved in 9.1 g of cold methyl iodide and kept for 3 days at $ca\ 20^{\circ}\text{C}$. The excess methyl iodide was evaporated *in vacuo* at 20°C and the resulting product dissolved in methylene chloride. The solution was washed with dilute aqueous sodium hydroxide solution, followed by water until neutral and then evaporated yielding 7-chloro-1,4-dimethyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine as a pale brown gum.

35 This base was purified by dissolving it in 1-N hydrochloric acid and extracting the resultant solution with ether to remove non-basic materials. The acid aqueous layer was then made basic with dilute sodium hydroxide solution and the precipitated product was extracted into methylene chloride. The extract was washed with water until neutral, dried over magnesium sulphate and evaporated yielding the purified base as a pale yellow gum. This was converted to the corresponding hydrochloride by dissolving it in methanol, adding 1.1 equivalents of 2-N methanolic hydrochloric acid, followed by precipitation of the hydrochloride by addition of ether and petroleum ether.

EXAMPLE 9

A) The preparation of the starting material

50 The 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No. 1,016,668).

B) The process

60 20 g of 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) in 500 ml of acetone were treated with 20 teaspoonsful ($ca\ 60\text{ g}$) of washed RANEY-nickel and heated under reflux for two hours. The washed RANEY-nickel was obtained by washing

RANEY-nickel (activity about W_2) thoroughly with water until the washings were neutral, then with ethanol and finally with acetone. The reaction mixture obtained was cooled, the RANEY-nickel filtered off and then washed with ethanol. The combined filtrates were evaporated, the residue dissolved in methylene chloride and the resulting solution washed with water, dried over magnesium sulphate and evaporated to yield a residue which was then dissolved in ether. The resulting ether solution was extracted with ice-cold 1-N hydrochloric acid solution and this aqueous solution then treated with dilute sodium hydroxide causing precipitation. The product was extracted into ether, the extract washed with water until neutral, dried over magnesium sulphate and evaporated to give a brown gum. This was then dissolved in methanol and 1.1 equivalents of 2-N hydrochloric acid in methanol added thereto. Ether and petroleum ether were added causing the precipitation of the hydrochloride of the reaction product. The hydrochloride was reconverted to free base by treatment with cold dilute sodium hydroxide solution and extraction of the free base into ether. The extracts, after washing with water and drying over magnesium sulphate, yielded the base on evaporation. The so-obtained crude product was recrystallized from (methylene chloride)/hexane and then from aqueous ethanol, forming yellow plates of 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine.

EXAMPLE 10

A) The preparation of the starting material

100 The 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No. 1,106,668).

B) The process

110 20 g of 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) in 500 ml of acetone were treated with 20 teaspoonsful ($ca\ 60\text{ g}$) of the washed RANEY-nickel described in example 9 and the resulting mixture was heated under reflux for two hours. The reaction mixture was then cooled and the RANEY-nickel filtered off and washed with ethanol. The combined filtrates were evaporated, the residue dissolved in methylene chloride, the resulting solution washed with water, dried over magnesium sulphate and evaporated. The residue was then dissolved in ether, the basic product extracted into ice-cold 1-N hydrochloric acid solution and then reprecipitated by the basification of the aqueous solution with dilute sodium hydroxide solution. The product was extracted into ether, the extract washed with water until neutral, dried over magnesium sulphate and evaporated. The residue was then dissolved in

methanol and 1.1 equivalents of 2-N hydrochloric acid in methanol added thereto. Ether and petroleum ether were then added causing the precipitation of 7-chloro-1-methyl-5-phenyl - 1,2 - dihydro - 3H - 1,4 - benzo - diazepine hydrochloride as orange needles. The hydrochloride was reconverted to the free base by treatment with cold dilute sodium hydroxide solution and extraction of the free base into ether. The extracts were washed with water, dried over magnesium sulphate, and evaporated yielding the free base which upon being recrystallized several times from pentane at -70°C gave very pale yellow prisms melting at $95^{\circ}\text{--}97^{\circ}\text{C}$.

The base was reconverted to the corresponding hydrochloride by treatment with methanolic hydrochloric acid followed by precipitation of the hydrochloride by addition of ether and petroleum ether. The hydrochloride so obtained, upon recrystallization from a mixture of methanol and ether, formed orange needles melting at $259^{\circ}\text{--}260^{\circ}\text{C}$.

EXAMPLE 11

A) The preparation of the starting material

The 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepine - thione-(2) starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No. 1,016,668).

B) The process

Washed RANEY-nickel was obtained as described in example 9. A mixture of 500 ml of acetone and 20 g of 7-chloro-5-(2-chlorophenyl) - 2,3 - dihydro - 1H - 1,4 - benzo - diazepinethione-(2) was treated with 20 teaspoonsful (ca 60 g) of the washer RANEY-nickel, then heated under reflux for two hours, cooled and the RANEY-nickel filtered off and washed with ethanol. The resulting filtrates were combined and evaporated, yielding a residue which was dissolved in methylene chloride. The resulting solution was washed with water, dried over magnesium sulphate and evaporated. The so-obtained residue was then dissolved in ether and the resulting solution extracted with ice-cold 1-N hydrochloric acid solution and the resulting aqueous solution then treated with dilute sodium hydroxide solution causing precipitation. The product was extracted into ether, the extract washed with water until neutral, dried over magnesium sulphate and evaporated to give a brown gum. This was dissolved in methanol, 1.1 equivalents of 2-N hydrochloric acid in methanol added to the resulting solution and precipitation effected by the addition of ether and petroleum ether. This yielded the hydrochloride of the reaction product, i.e. 7-chloro-5-(2-chloro-phenyl) - 1,2 - dihydro - 3H - 1,4-benzodiazepine hydrochloride, which was reconverted to the free base by treatment with cold dilute sodium hydroxide solution and

extraction of the free base into ether. The extracts, after washing with water and drying over magnesium sulphate, yielded the base on evaporation. The latter was recrystallized from benzene/hexane and formed pale yellow prisms of melting point $174^{\circ}\text{--}175^{\circ}\text{C}$.

EXAMPLE 12

To a suspension of 2.5 g of lithium aluminium hydride in 1000 ml of absolute ether were added 10 g of 7-chloro-5-(2-chlorophenyl) - 1,2,4,5 - tetrahydro - 3H - 1,4 - benzodiazepinone-(2) and the mixture was heated under reflux for 21 hours. After the dropwise addition of 50 ml of water to the stirred and cooled suspension, the ether solution was dried with sodium sulphate and filtered. The ether was evaporated and the residue treated with 50 ml of a 16% solution of hydrogen chloride in ethanol. The solvent was removed *in vacuo* on a steam-bath, the residue dissolved in ethanol and the solvent again evaporated as previously described in order to remove the excess hydrogen chloride. The residue was recrystallized three times from a mixture of ethanol and ether yielding 7 - chloro - 5 - (2 - chloro - phenyl) - 1,2,4,5 - tetrahydro - 3H - 1,4 - benzodiazepine hydrochloride as white needles which melted at $275^{\circ}\text{--}280^{\circ}\text{C}$ under decomposition.

EXAMPLE 13

A) The preparation of the starting material:

The N - [2 - (4 - chloro - 2 - benzoyl - anilino)-ethyl]-benzamide starting material was prepared as described in the specification of our copending Application for Letters Patent No. 37642/64 (now Serial No. 1,016,667).

B) The process:

A solution of 1.1 g of N-[2-(4-chloro-2-benzoyl-anilino)-ethyl]-benzamide in a mixture of 15 ml of concentrated hydrochloric acid and 10 ml of ethanol was heated on the steam-bath for 56 hours. The reaction mixture was diluted with water and extracted with methylene chloride. The aqueous layer, which contains 5-chloro-2-aminoethylaminobenzophenone hydrochloride, was made alkaline with 3-N potassium hydroxide and extracted with methylene chloride. The resulting organic layer was dried and concentrated *in vacuo* to dryness. The residue was crystallized from ether yielding 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine.

EXAMPLE 14

A) The preparation of the starting material

The N - [2 - (4 - chloro - 2 - benzoyl - anilino)-ethyl]-phthalimide was prepared as described in the specification of our copending Application for Letters Patent No. 37642/64 (now Serial No.).

B) The process

To 30 ml of 70% sulphuric acid heated to

135°C was added 1 g of N-[2-(4-chloro-2-benzoyl-anilino)-ethyl]-phthalimide. The temperature was raised to 179°C. After 0.5 hour the solution was poured over ice and extracted with methylene chloride. The aqueous layer, which contains 5-chloro-2-aminoethylamino-benzophenone sulphate, was made alkaline with 40% potassium hydroxide and extracted with methylene chloride. The resulting organic layer was dried and concentrated *in vacuo* to dryness. The residue was crystallized from ether yielding 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine.

EXAMPLE 15

15 A) *The preparation of the starting material*
24 g of 7-chloro-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) were placed in a 500 ml three-necked round-bottomed flask fitted with a stirrer and a reflux condenser. The compound was then dissolved in 100 ml of N,N-dimethyl-formamide and the sodio derivative prepared by warming and stirring the resulting solution with 23.9 ml of a solution of sodium methoxide in methanol (0.0044 m/ml) for 1 hour. 125.4 g of methyl iodide were then added and the resulting solution stirred for 1 hour at ca 20°C and then for 7 hours at about 50°C. The solvent was distilled off under reduced pressure and the residue dissolved in 250 ml of methylene chloride. This solution was washed with 150 ml of water, 150 ml of 3-N hydrochloric acid, 150 ml of water, and 3 times with 50 ml of saturated brine solution. The methylene chloride solution was then dried over anhydrous sodium sulphate, the solvent removed and the residual oil taken up in 200 ml of ether. The ether solution was then filtered through a layer of 50 g of WOELM alumina (neutral, grade I) which was thoroughly eluted with ether until the ether washings were colourless. The ether fractions were then combined and the solvent removed, yielding a pale yellow oil which was crystallized and recrystallized from hexane to yield 7-chloro-1,4-dimethyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) melting at 90°—91°C.

B) *The process*

50 A solution of 5.0 g of 7-chloro-1,4-dimethyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) in 100 ml of ether was treated with 0.95 g of lithium aluminium hydride and the resulting mixture stirred under reflux for 3 hours. Excess lithium aluminium hydride was then destroyed by the addition of a mixture of ether and ethyl acetate (1:1). A saturated solution of potassium bicarbonate in water was added until the resultant grey solid coagulated. This was filtered off and washed thoroughly with ether. The ether washings and filtrates were combined, washed with 50 ml of water and dried over anhydrous sodium sulphate. Filtration and removal of

the solvent gave a pale yellow oil which was dissolved in a small amount of methanol and the resulting solution treated with an excess of methanolic hydrochloric acid solution. The solvent was removed under reduced pressure and the residual hydrochloride recrystallized twice from acetone yielding white prisms of 7-chloro-1,4-dimethyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine hydrochloride melting at 225°—228°C.

A small amount of the above hydrochloride was dissolved in water, the resulting solution made alkaline with ammonium hydroxide and the base extracted into methylene chloride. The methylene chloride solution was washed ammonia free with water, dried over anhydrous sodium sulphate, filtered, and the solvent removed. The residue was recrystallized from ethanol yielding 7-chloro-1,4-dimethyl-1,2,4,5-tetrahydro-5-phenyl-3H-1,4-benzodiazepine as white prisms melting at 79°—80°C.

EXAMPLE 16.

A) *The preparation of the starting material.*

A stirred solution of 75 g of 2-amino-2'-nitro-benzophenone in 700 ml of hot concentrated hydrochloric acid was cooled to 0°C and a solution of 21.5 g of sodium nitrite in 50 ml of water added in the course of 3 hours. The temperature of the suspension was kept at 2°—7°C during the addition. The resulting clear solution was poured into a stirred solution of 37 g of cuprous chloride in 350 ml of hydrochloric acid (1:1). The solid which had formed after a few minutes was filtered off, washed with water and recrystallized from ethanol. Crystals of 2-chloro-2'-nitro-benzophenone melting at 76°—79°C were obtained.

A solution of 20 g of 2-chloro-2'-nitro-benzophenone in 450 ml of ethanol was hydrogenated at normal pressure and ca 20°C using RANEY nickel. After the uptake of ca 6 litres of hydrogen, the catalyst was filtered off and the alcohol then removed *in vacuo*. The residue was distilled in a bulb tube at 0.4 mm and at bath temperature of 150°—165°C giving a yellow oil. The oil was dissolved in alcohol and, on addition of water, needles of 2-amino-2'-chloro-benzophenone melting at 58°—60°C were obtained.

To a solution of 42 g of 2-amino-2'-chloro-benzophenone in 500 ml of benzene were added dropwise 19 ml of bromo-acetyl bromide. After heating under reflux for 2 hours, the solution was cooled, washed with 2-N sodium hydroxide and evaporated. The residue was recrystallized from methanol giving crystals of 2-bromo-2'-(2-chloro-benzoyl)-acetanilide melting at 119°—121°C.

To a solution of 14.5 g of the foregoing acetanilide in 100 ml of tetrahydro-furan was added an excess of liquid ammonia (ca 150 ml). The ammonia was kept under reflux with a dry-ice condenser for 3 hours after which time the ammonia was allowed to

evaporate and the solution was poured into water. Crystals of 2-amino-2¹-(2-chloro-benzoyl)-acetanilide were collected which melted at 162°—164°C after crystallization from ethanol.

- 5 A solution of 3 g of 2-amino-2¹-(2-chloro-benzoyl)-acetanilide in 50 ml of pyridine was heated under reflux for 24 hours after which time the pyridine was removed *in vacuo*. The residue was recrystallized from methanol and a mixture of dichloro-methane and ether giving crystals of 5-(2-chloro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) melting at 212°—213°C.

15 B) *The process*

- 8 g of 5-(2-chloro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) contained in a SOXHLET extractor were slowly extracted into a boiling solution of 5.7 g of lithium aluminium hydride in 500 ml of ether. After 20 hours the solution was cooled and the excess lithium aluminium hydride destroyed by the addition of ethyl acetate and water. After drying with sodium sulphate, the solvent was removed and the crystalline residue recrystallized from benzene yielding yellow platelets of 5-(2-chloro-phenyl)-1,2-dihydro-3H-1,4-benzodiazepine melting at 165°—167°C.

30 EXAMPLE 17

A) *The preparation of the starting material.*

- The 7-chloro-1,4-dimethyl-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) starting material was prepared as described in the specification of our Letters Patent No. 988,634.

B) *The process*

- 0.9 g of lithium aluminium hydride were added to a solution of 5.0 g of 7-chloro-1,4-dimethyl-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) in 50 ml of anhydrous ether and the mixture was stirred under reflux for 3 hours. Excess lithium aluminium hydride was then destroyed by the addition of a mixture of ether and ethyl acetate (1:1). A saturated solution of potassium bicarbonate was added until a solid coagulated. This was filtered off and washed thoroughly with ether. The ether washings and filtrate were combined, washed with 50 ml of water and dried over anhydrous sodium sulphate. Filtration and removal of the solvent yielded an oil which was dissolved in a small volume of methanol. The solvent was removed under reduced pressure and the residue recrystallized from methanol yielding colourless prisms of 7-chloro-1,4-dimethyl-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine melting at 68°—70°C.

60 EXAMPLE 18

A) *The preparation of the starting material*

The 7-chloro-5-(3-fluoro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-

(2) starting material was prepared as described in the specification of our Letters Patent No. 972,968.

B) *The process*

2.3 g of 7-chloro-5-(3-fluoro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) were placed in the thimble of a SOXHLET extractor mounted on a 500 ml round-bottom flask used as the boiler. A solution of 0.6 g of lithium aluminium hydride in 250 ml of anhydrous ether was placed in the boiler and the benzodiazepinone extracted into the reaction mixture over a period of 18 hours. After excess lithium aluminium hydride had been decomposed by the careful addition of ethyl acetate, a saturated solution of 75 ml of ammonium chloride was added and the coagulated solid material filtered off. The precipitate was washed twice with 50 ml of ether each time and the combined filtrates separated. The aqueous layer was washed twice with 50 ml of ether each time and the combined ether layers were then washed with 75 ml of water, twice with 25 ml of saturated brine each time and dried over anhydrous sodium sulphate. Hydrogen chloride was bubbled into the ethereal solution of the base, the precipitated hydrochloride was filtered and recrystallized from a mixture of methanol and ether yielding 7-chloro-5-(3-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepine hydrochloride as colourless prisms of melting point 283.5°—285°C.

EXAMPLE 19

A) *The preparation of the starting material*

The 5-(4-chloro-phenyl)-1-methyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No. 1,016,668).

B) *The process*

A solution of 5.2 g of 5-(4-chloro-phenyl)-1-methyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) in 100 ml of acetone was heated under reflux for 3 hours with RANEY-nickel (5 teaspoonsful, ca 40 g of wet nickel). The mixture was then allowed to stand for 48 hours at ca 20°C and filtered over a diatomaceous earth filter aid. Solvents were removed, the residue was taken up in 2-N hydrochloric acid and washed once with ether. The base was precipitated with ammonium hydroxide and extracted into three 50 ml portions of methylene chloride. The organic fractions were combined, washed twice with 50 ml of water each time, dried over anhydrous sodium sulphate, filtered and evaporated. The residual oil was dissolved in ether and filtered through 50 g of grade I, neutral alumina. Removal of the solvent and crystallization from hexane gave 1-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine as white rods of melting point 113°—115°C.

The mother liquors were concentrated and the precipitated products consisting of 1-methyl - 5 - phenyl - 1,2 - dihydro - 3H - 1,4-benzodiazepine as white rods and 5-(4-chloro - phenyl) - 1 - methyl - 1,2 - dihydro - 3H-1,4-benzodiazepine as yellow prisms were mechanically separated to give yellow prisms of 5 - (4 - chloro - phenyl) - 1 - methyl - 1,2 - dihydro - 3H-1,4-benzodiazepine which, upon being recrystallized from methanol, melted at 151°—153°C.

EXAMPLE 20

A solution of 3.1 g of 7-chloro-4-methyl-5 - phenyl - 1,2,4,5 - tetrahydro - 3H - 1,4 - benzodiazepinone-(2) in 75 ml of pure tetrahydro-furan was added to a solution of 0.82 g of lithium aluminium hydride in 100 ml of pure tetrahydro-furan. The mixture was heated under reflux with stirring for 4 hours on a steam-bath and then cooled. Excess lithium aluminium hydride was decomposed with a mixture of ethyl acetate and ether (1:1) and a saturated potassium bicarbonate solution was then added until the solid coagulated. This was filtered using suction and the filter cake washed thoroughly with ether. The combined filtrates were washed three times with 100 ml of water each time, dried over anhydrous sodium sulphate and filtered over 10 g of grade I neutral alumina. The solvent was removed and the residue crystallized from an ether/(petroleum ether) mixture to give the product, 7-chloro-4-methyl-5-phenyl-1,2,4,5 - tetrahydro - 3H - 1,4 - benzodiazepine, as colourless prisms melting at 107°—109°C. The base was dissolved in ether and hydrogen chloride bubbled in until precipitation was complete. The salt was filtered off and recrystallized from an acetone/ether mixture to give the hydrochloride as white prisms melting at 155°—175°C.

EXAMPLE 21.

A suspension of 126.5 g of 1-methyl-7-nitro - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine [obtained in the form of yellow prisms of melting point 187°—188°C (from a mixture of methylene chloride and ether) by N¹-methylation of the 7-nitro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine described in Example 22 hereinafter] in 2.2 litres of methanol was hydrogenated at ca 20°C and atmospheric pressure in the presence of 5 tablespoonsful of RANEY-nickel. After the absorption of 1.35 mol of hydrogen (3 hours) the RANEY-nickel was filtered off, the filtrate acidified with an excess of methanolic hydrogen chloride and the solution concentrated to a smaller volume *in vacuo*, with stirring. Ether was added and the precipitated crystals were filtered off giving orange prisms of 7-amino - 1 - methyl - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine dihydrochloride which, after recrystallization from a

mixture of methanol and ether, melted at 267°—268°C.

An ice-cold solution of 20 g of 7-amino-1-methyl - 5 - phenyl - 1,2 - dihydro - 3H - 1,4-benzodiazepine dihydrochloride in water was made alkaline with 50% potassium hydroxide and extracted with methylene chloride. The organic layer was separated, dried, concentrated to a small volume and treated with petroleum ether. The crystalline base, 7-amino - 1 methyl - 5 - phenyl - 1,2 - dihydro - 3H-1,4-benzodiazepine, was separated by filtration and recrystallized from ether to form yellow prisms melting at 158°—159°C. This compound is useful, *inter alia*, as an appetite depressant.

The 7-amino substituent in the benzodiazepine dihydrochloride prepared according to the first paragraph of this example may be converted into an acetamido, chloro or cyano substituent as follows:

i) A solution of 1.6 g of 7-amino-1-methyl-5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine dihydrochloride in a mixture of 20 ml of pyridine and 10 ml of acetic anhydride was left at ca 20°C for 60 hours. The precipitated crystalline hydrochloride reaction product was separated by filtration and dissolved in ice-water. The base was liberated by treatment with dilute sodium hydroxide and extracted with methylene chloride. The organic layer was dried, concentrated *in vacuo* and the residue crystallized from ether, yielding 7 - acetamido - 1 - methyl - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine which, after recrystallization from a mixture of methylene chloride and petroleum ether, formed yellow prisms melting at 176°—177°C.

ii) To a stirred solution (cooled to 0°—5°C) of 12.4 g of 7-amino-1-methyl-5-phenyl-1,2 - dihydro - 3H - 1,4 - benzodiazepine dihydrochloride in 40 ml of 1-N hydrochloric acid were added within 10 minutes 40 ml of 1-N aqueous sodium nitrite. The diazonium chloride solution which formed was added within 10 minutes to a stirred solution (heated to 80°—90°C) of 3.8 g of cuprous chloride in 70 ml of concentrated hydrochloric acid which had been diluted with 35 ml of water. The mixture was kept for a further 10 minutes at 80°—90°C and was then cooled. Ice, water and an excess of ammonium hydroxide were added and the reaction product then extracted with methylene chloride. The organic layer was dried, concentrated *in vacuo* to dryness and the residue was dissolved in methanol. An excess of methanolic hydrogen chloride was added and the solution was concentrated *in vacuo* to dryness. Isopropanol was added to the residue and the crude reaction product was separated by filtration. This product was repeatedly crystallized from isopropanol yielding 7 - chloro - 5 - phenyl - 1 - methyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine hydro-

chloride melting at 250°—251°C (with decomposition). It was identical with a sample prepared according to the procedure set forth in Example 10.

- 5 iii) To a stirred solution (cooled to 0°—5°C) of 12.4 g of 7-amino-1-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine dihydrochloride in 40 ml of 1-N hydrochloric acid were added within 10 minutes 40 ml of
10 1-N sodium nitrite. The diazonium chloride solution formed was added within 12 minutes to a stirred suspension (heated to 80°—90°C) of 8 g of cuprous cyanide in 300 ml of N,N-dimethyl-formamide. The reaction mixture
15 was cooled to 60°C, diluted with 200 ml of 58% ammonium hydroxide and extracted with benzene. The organic layer was dried and concentrated *in vacuo*. The residue was extracted with boiling ether and the ether solution
20 filtered and concentrated *in vacuo* to yield an oily residue which was dissolved in 80 ml of ether and adsorbed on a chromatographic column prepared with 140 g of WOELM alumina (grade I). The product was
25 then eluted with ether. Concentration of the first 750 ml of eluant yielded an oil which crystallized from a mixture of ether and petroleum ether and was recrystallized from ether, yielding 7-cyano-1-methyl-5-phenyl-
30 1,2-dihydro-3H-1,4-benzodiazepine as slightly yellow plates melting at 149°—150°C.

EXAMPLE 22.

- 2.7 g of 7-nitro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine [obtained in the form of
35 yellow needles of melting point 211°—212°C (from acetone) by reacting 2-amino-5-nitro-benzophenone with ethyleneimine in accordance with the procedure described in Example 2] dissolved in 100 ml of methanol were
40 hydrogenated at *ca* 20°C and atmospheric pressure in the presence of 3 g of wet RANEY-nickel. After 1 hour, 0.03 mol of hydrogen had been absorbed and the uptake came to a complete standstill. The catalyst
45 was removed by filtration and the solution concentrated *in vacuo* to dryness. The residue was dissolved in methanol and acidified with an excess of methanolic hydrogen chloride. The crystalline 7-amino-5-phenyl-1,2-dihydro-
50 3H-1,4-benzodiazepine dihydrochloride was precipitated by the addition of ether and, after recrystallization from a mixture of methanol and ether, formed yellow needles melting above 250°C.

EXAMPLE 23.

- 55 i) A suspension of 28.1 g of 3-methyl-7-nitro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine [obtained in the form of yellow plates of melting point 249°—250°C (from methylene chloride) by reacting 2-amino-5-nitro-benzophenone with 2-methyl-ethyleneimine in accordance with the procedure described in Example 2] in 250 ml of

methanol was hydrogenated at *ca* 20°C and atmospheric pressure in the presence of 6 g of wet RANEY-nickel catalyst. After the absorption of 0.3 mol of hydrogen, the reaction came to a complete stop. The catalyst was filtered off, the filtrate acidified with an excess of methanolic hydrogen chloride and concentrated *in vacuo* to dryness. Ethanol was added to the residue and the crude reaction product was separated by filtration. Recrystallization from a mixture of ethanol and ether yielded 7-amino-3-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine dihydrochloride as yellow prisms which darkened at 265°C and melted at 277°—280°C (with decomposition). The base was liberated from the hydrochloride by treatment with alkali. It crystallized from ether in brown prisms melting at 128°—129°C.

ii) To a cooled stirred solution of 6.4 g of 7-amino-3-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine dihydrochloride in 30 ml of 6-N hydrochloric acid were added within 10 minutes 20 ml of 1-N sodium nitrite solution while the temperature was kept below 5°C. The solution was stirred an additional 15 minutes at 0°C and then added within 5 minutes to a stirred solution (28°C) of 4 g of cuprous chloride in 40 ml of concentrated hydrochloric acid. The mixture was stirred at *ca* 20°C for 0.25 hour, heated to 40°C for 0.5 hour and then heated to 85°—90°C for 20 minutes. The reaction mixture was then cooled, treated with an excess of ammonium hydroxide and extracted with methylene chloride. The organic layer was dried, concentrated *in vacuo* and the residue dissolved in ether and filtered by gravity through 60 g of WOELM alumina(I). The first 250 ml of ether gave upon concentration an oily residue which was crystallized from a mixture of ether/(petroleum ether) and yielded a crystalline reaction product which upon one recrystallization from the same solvent mixture melted at 126°—127°C. The reaction product gave no melting point depression with a sample of the product prepared according to the method set forth in Example 24 hereinafter and also showed an identical infrared spectrum.

EXAMPLE 24.

To a stirred suspension of 0.76 g of lithium aluminium hydride in 25 ml of dry tetrahydro-furan was added a solution of 2.84 g of 7-chloro-3-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone (2) in 50 ml of tetrahydro-furan. The reaction mixture was heated under reflux for 25 minutes, then cooled with ice and treated with ether saturated with water. The insoluble precipitate was separated by filtration, the filtrate dried and concentrated *in vacuo*. The residue was dissolved in 0.1-N hydrochloric acid and the solution filtered by gravity. The filtrate was

made alkaline with dilute sodium hydroxide and extracted with methylene chloride. The organic layer was separated, dried and concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of ether and petroleum ether and the crude reaction product was separated by filtration. Recrystallization from the same solvent mixture yielded 7-chloro-3-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine as pale yellow prisms melting at 127°—128°C.

EXAMPLE 25.

A) *The preparation of the starting material.*

The 1-methyl-5-(2-trifluoromethyl-phenyl)-2,3-dihydro-1H-1,4-benzodiazepin-2(1H)-one starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No. 1,016,668).

B) *The process.*

10 mmol of 1-methyl-5-(2-trifluoromethyl-phenyl)-2,3-dihydro-1H-1,4-benzodiazepin-2(1H)-one were dissolved in 80 ml of acetone and treated with 3.3 teaspoonsful of washed RANEY-nickel (i.e. ca 27 g of settled RANEY-nickel when weighed wet with ethanol; prepared according to the procedure set forth in example 10) and then heated under reflux for 2 hours with stirring. The mixture was then cooled and the mixture filtered and the solid residue washed with ethanol. The combined filtrates were evaporated and the residue was dissolved in a mixture of 100 ml of ice-cold aqueous 1-N hydrochloric acid and 100 ml of ether. The aqueous layer was rendered basic with sodium hydroxide solution and extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulphate and evaporated yielding a crude crystalline product which was dissolved in methanolic 2-N hydrochloric acid (1.1 equivalents). The resulting solution was evaporated, the residue triturated with ether and filtered to give orange-yellow prisms of 1-methyl-5-(2-trifluoromethyl-phenyl)-1,2-dihydro-3H-1,4-benzodiazepine hydrochloride. These prisms were crystallized from ethanol/ether and reconverted to the free base by treatment with a dilute sodium hydroxide solution and ether. The ether layer was washed with water, dried over anhydrous magnesium sulphate and evaporated, yielding cream-coloured prisms which, upon recrystallization from hexane, formed colourless prisms of the free base, 1-methyl-5-(2-trifluoromethyl-phenyl)-1,2-dihydro-3H-1,4-benzodiazepine, melting at 83°—85°C. The pure base was reconverted to the corresponding hydrochloride by addition of methanolic hydrochloric acid. Upon recrystallization from ethanol/ether, the hydrochloride formed bright yellow prisms melting at 251°—252°C.

EXAMPLE 26

A) *The preparation of the starting material.*

The 7-dimethylamino-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2(1H)-one starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No. 1,016,668).

B) *The process*

10 ml of 7-dimethylamino-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2(1H)-one were treated with RANEY-nickel according to the procedure described in Example 25. The crude crystalline product was converted to the dihydrochloride by dissolution in 2.2 equivalents of methanolic 1-N hydrochloric acid followed by precipitation by the addition of ether. There was thus obtained 7-dimethylamino-1-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine dihydrochloride as orange prisms which were recrystallized from methanol/ethanol/ether. The purified crystals obtained were then treated with dilute sodium hydroxide and ether. The ether layer was washed with water, dried over anhydrous magnesium sulphate and evaporated. The resulting residue was twice recrystallized from aqueous ethanol yielding the free base, 7-dimethylamino-1-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine, as hexagonal plates melting at 115°—117°C. The free base was reconverted to the dihydrochloride by treatment with methanolic hydrochloric acid. Upon recrystallization from ethanol/ether the dihydrochloride melted at 252°—254°C.

EXAMPLE 27

A) *The preparation of the starting material*

The 7-bromo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2(1H)-one starting material was prepared as described in the specification of our Letters Patent No. 972,968.

B) *The process*

A suspension of 1.20 g of lithium aluminium hydride in 100 ml of anhydrous tetrahydrofuran was stirred and heated under reflux for 0.5 hour, with protection from atmospheric moisture. The mixture was then cooled to ca 20°C and 15.6 mmol of 7-bromo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2(1H)-one in 150 ml of anhydrous tetrahydrofuran were added thereto as rapidly as the vigorous reaction permitted (i.e. in the course of about 10 minutes). The mixture was then stirred and heated under reflux on a steam-bath for 4 minutes, allowed to cool spontaneously for another 5 minutes and then rapidly cooled in an ice-bath. The reaction mixture was then permitted to stand for a further 0.75 hour at 25°—27°C and then the mixture was stirred and cooled in an ice-bath during the dropwise addition of 10 ml of a saturated aqueous solution of sodium sulphate to decompose

excess of lithium aluminium hydride. Stirring was continued for 1 hour at *ca* 20°C followed by the addition of anhydrous sodium sulphate to dry the solution. The insoluble inorganic salts were then filtered off on a bed of diatomaceous earth filter aid and were thoroughly washed with ether. The combined filtrates were then evaporated *in vacuo* yielding a crude product which was dissolved in 300 ml of ether. This was then extracted with 100 ml of 1-*N* hydrochloric acid and then with 80 ml of 1-*N* hydrochloric acid. The acid extracts were combined, cooled in an ice-bath and rendered basic by the addition of 3-*N* sodium hydroxide solution. The resulting precipitated product was extracted with ether, the extract washed with water until neutral, dried over anhydrous magnesium sulphate and evaporated. The residue was dissolved in a small volume of cold methanol and 1.1 equivalents of methanolic 2-*N* hydrochloric acid added thereto. The resulting solution was evaporated *in vacuo* at 25°C and the residue was recrystallized from ethanol/ether. The hydrochloride obtained was then reconverted to the free base by treatment with dilute aqueous sodium hydroxide and extraction with ether. The extract was washed with water until neutral, dried over magnesium sulphate and evaporated to yield a yellow crystalline residue which was crystallized from aqueous ethanol. This yielded 7-bromo - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine as yellow plates melting at 172°—175°C.

EXAMPLE 28

15.6 mmol of 7-chloro-5-(2-fluoro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) were treated with lithium aluminium hydride as described in example 27. As described therein, the base was converted into the hydrochloride and the hydrochloride then reconverted to the base giving, upon evaporation, the product in the form of a yellow foam which was crystallized from aqueous ethanol yielding 7-chloro - 5 - (2 - fluoro - phenyl) - 1,2 - dihydro - 3H - 1,4 - benzodiazepine as yellow prisms melting at 160°—163°C.

EXAMPLE 29

A) *The preparation of the starting material*
The 7 - methylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) starting material was prepared as described in the specification of our Letters Patent No. 972,968.

B) *The process*
5.0 g of 7-methylmercapto-5-phenyl-2,3-dihydro - 1H - 1,4 - benzodiazepinone - (2) were dissolved in 200 ml of anhydrous tetrahydro-furan and treated with 2.0 g of lithium aluminium hydride. The mixture was then stirred and heated under reflux for 2.5 hours,

with protection from atmospheric moisture. The excess lithium aluminium hydride was decomposed by the dropwise addition of 10 ml of saturated aqueous sodium sulphate solution to the cooled reaction mixture. The solution was then dried with anhydrous sodium sulphate, the undissolved inorganic salts filtered off and washed with ether, and the combined filtrates and washings evaporated *in vacuo*. This yielded the crude product as an oil which was dissolved in 13 ml of methanol and treated with 13 ml of methanolic 1.46-*N* hydrochloric acid. This was followed by dilution with ether and hexane to precipitate the hydrochloride of 7-methylmercapto - 5 - phenyl - 1,2,4,5 - tetrahydro - 3H-1,4-benzodiazepine as pale yellow prisms which were treated with dilute aqueous sodium hydroxide and extracted with ether. The extract was washed with water until neutral, dried over magnesium sulphate and evaporated. The residue was then recrystallized from hexane yielding the base, 7-methylmercapto - 5 - phenyl - 1,2,4,5 - tetrahydro - 3H-1,4-benzodiazepine, as colourless prisms melting at 101°—103°C.

EXAMPLE 30

A) *The preparation of the starting material*
The 7 - methyl - 5 - phenyl - 2,3 - dihydro-1H - 1,4 - benzodiazepinethione - (2) starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No.).

B) *The process*

2.66 g of 7-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinethione-(2) were dissolved in 80 ml of acetone and desulphurised by heating the solution under reflux with RANEY-nickel as described in example 25. This yielded the crude base as a brown gum. This was converted to the hydrochloride by dissolving it in 1.1 equivalents of methanolic 2-*N* hydrochloric acid, followed by evaporation of the resulting solution and recrystallization of the residue from isopropanol/acetone/ether. The resulting impure hydrochloride was reconverted to the base by treatment with dilute aqueous sodium hydroxide and extraction with ether. The extract was dried over anhydrous magnesium sulphate and evaporated, yielding the purified base as a light brown gum which was dissolved in methylene chloride and chromatographed through 50 g of WOELM alumina (neutral, activity III). Elution with methylene chloride and evaporation of the eluate gave the desired product as a pale brown gum which soon started to crystallize. Recrystallizations from hexane and then from aqueous ethanol, gave 7-methyl-5-phenyl-1,2-dihydro - 3H - 1,4 - benzodiazepine as yellow plates of melting point 130°—132°C.

EXAMPLE 31

A) *The preparation of the starting material*

5 The 7-chloro-5-(2-methoxy-phenyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-thione-(2) starting material was prepared as described in the specification of our copending application for Letters Patent No. 37643/64 (now Serial No.).

B) *The process*

10 3.17 g of 7-chloro-5-(2-methoxy-phenyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-thione-(2) were dissolved in 80 ml of acetone and desulphurised by heating the solution under reflux with RANEY-nickel as described in example 25. This yielded the crude base as a tan-coloured foam which was dissolved in methylene chloride and chromatographed over 50 g of WOELM alumina (neutral activity III).

20 Elution with methylene chloride gave only a trace of gum. Further elution with (methylene chloride)/methanol (100:1) and evaporation of the eluate yielded the desired base as a yellow gum which partly crystallized. 25 Recrystallization from acetone/(petroleum ether) (boiling point 40°—60°C) gave the product 7-chloro-5-(2-methoxy-phenyl)-1,2-dihydro-3H-1,4-benzodiazepine as yellow prisms which, upon further recrystallization from aqueous ethanol, formed yellow flat prisms melting at 190°—191°C.

EXAMPLE 32.

35 20.0 g of 5-phenyl-7-trifluoromethyl-1,2-dihydro-3H-1,4-benzodiazepine [obtained in the form of yellow needles of melting point 110°—111°C (from hexane) by reacting 2-amino-5-trifluoromethyl-benzophenone with ethylenimine in accordance with the procedure described in Example 2] were dissolved in 200 ml of aqueous 3-N hydrochloric acid and the solution was stirred and heated under reflux for 10 hours. After cooling the mixture at 0°C for 16 hours the resulting yellow crystalline product was filtered off, washed with 20 ml of ice-cold aqueous 3-N hydrochloric acid and dried *in vacuo* at 25°C over phosphorus pentoxide and potassium hydroxide pellets. 7 g of this product [2-aminoethylamino-5-carboxy-benzophenone hydrochloride] were dissolved in 142 ml of hot pyridine and the solution heated at the reflux temperature for 3 hours. During this time a yellow crystalline product commenced to precipitate. The mixture was evaporated 55 *in vacuo* and the resulting yellow crystalline residue was recrystallized from methanol/ether to give crude 7-carboxy-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine hydrochloride monohydrate as orange-yellow needles which, upon further recrystallizations from methanol/ether and from water, formed flat yellow prisms melting at 315°—316°C (with decomposition).

65 2.56 g of the foregoing benzodiazepine hydrochloride monohydrate were dissolved in 50 ml of methanol and this solution was added

portionwise to a solution of ca 3 g of freshly distilled diazo-methane in 200 ml of ether at 0°C. The homogeneous yellow solution was kept for 1 hour at 0°C—5°C and then the mixture was stirred in an ice-bath while 50 ml of aqueous 1-N hydrochloric acid were added dropwise. The mixture was then diluted with 150 ml of water and then the aqueous acid layer was separated, cooled and made basic by addition of aqueous 3-N sodium hydroxide. The resulting suspension was extracted with ether, the extract washed with water, dried over anhydrous magnesium sulphate and evaporated to give the product as a light yellow crystalline residue which, upon recrystallizations from (methylene chloride)/[petroleum ether (40—60°C)] and from aqueous ethanol, then yielded the desired 7-methoxycarbonyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine as very pale yellow flat prisms melting at 191°—193°C.

EXAMPLE 33

A) *The preparation of the starting material*

A mixture of 20.0 g of 7-chloro-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2), 25.0 ml of acetic anhydride 25.0 g of hydrated sodium acetate was warmed on a steam-bath at 60°—70°C for 16 hours. 300 ml of hot water were then added slowly and the mixture cooled to ca 20°C. The product was filtered giving colourless plates which, upon recrystallization from an acetone/cyclohexane mixture gave 4-acetyl-7-chloro-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) as a dimorphous compound melting at 122°C resetting by 140°C and melting sharply at 203°—204°C.

A solution of 5.0 g of the foregoing benzodiazepinone in 25 ml of N,N-dimethylformamide was heated with 4.15 ml of a solution of sodium methoxide in methanol (4.15 ml of solution contains 0.235 g of sodium methoxide). The resulting clear solution was cooled to -2°C and 1.8 ml (3.37 g) of ethyl iodide were added. The reaction mixture was allowed to warm to ca 20°C, stirred for 1 hour and then diluted with 500 ml of water. The product was filtered, washed with water and recrystallized from methanol giving colourless prisms of 4-acetyl-7-chloro-1-ethyl-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) melting at 180°—181°C.

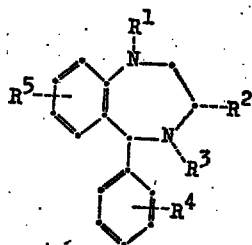
B) *The process*

A solution of 2.0 g of 4-acetyl-7-chloro-1-ethyl-5-(2-fluoro-phenyl)-1,2,4,5-tetrahydro-3H-1,4-benzodiazepinone-(2) in 50 ml of anhydrous tetrahydro-furan was added slowly to a stirred suspension of 0.85 g of lithium aluminium hydride in 30 ml of tetrahydro-furan. The reaction mixture was heated under reflux for 4 hours and excess lithium aluminium hydride was then decomposed with an ethereal ethyl acetate solution. Saturated

- aqueous potassium bicarbonate was added until a solid coagulate had formed. The organic phase was filtered, the precipitate washed with ether and the combined filtrates were taken to dryness. The residual oil was dissolved in 100 ml of ether and the solution washed five times with 100 ml of water each time, dried over anhydrous sodium sulphate, filtered and saturated with hydrogen chloride.
- The hydrochloride salt was filtered off and recrystallized from an acetone/ether mixture giving colourless prisms. The hydrochloride was reconverted to the base by dissolution in water and making the solution alkaline with dilute sodium hydroxide. The base was filtered off, dissolved in petroleum ether (boiling point = 30°—60°C), dried over anhydrous sodium sulphate, filtered, concentrated to a small volume and allowed to crystallize, yielding 7-chloro - 1,4 - diethyl - 5 - (2 - fluoro-phenyl) - 1,2,4,5 - tetrahydro - 3H - 1,4 - benzodiazepine melting at 92°—94°C.

WHAT WE CLAIM IS:—

- 1) Compounds of the general formula



25

- wherein R¹ and R³ represent lower alkyl, lower alkenyl or lower alkanoyl groups, R² represents a lower alkyl group, R⁴ and R⁵ represent halogen atoms or trifluoro-methyl, nitro, amino lower alkanoylamino, lower alkylthio, lower alkoxy, lower alkyl, cyano, carboxy, lower alkoxy-carbonyl or di(lower alkyl)-amino groups and the broken lines denote that the R-substituents attached thereby are optional, and 4,5-dehydro derivatives thereof in which R³ is absent, and acid-addition salts of the basic compounds and basic derivatives.

- 2) Substances as claimed in claim 1, wherein one or both of the substituents R⁴ and R⁵ are present and represent halogen atoms or trifluoro-methyl, nitro, lower alkylthio, cyano, amino or di(lower alkyl)-amino groups.

- 3) Substances as claimed in claim 1 or claim 2, which are substituted in the 7- and/or 2¹-position.

- 4) Substances as claimed in claim 3, wherein the substituents are halogen atoms or trifluoro-methyl or amino groups.

- 5) 4,5-Dehydro derivatives of the com-

pounds formulated in claim 1 in which R³ is absent, wherein R¹ is present and represents a lower-alkyl group, R² and R⁴ are absent and R⁵ is present in the 7-position and represents a halogen atom.

- 6) 7 - Chloro - 1 - methyl - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine.

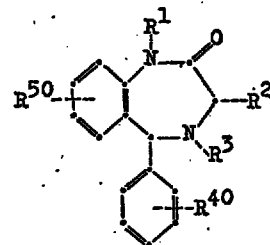
- 7) 7 - (Trifluoro - methyl) - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine.

- 8) 7 - Nitro - 5 - phenyl - 1,2 - dihydro - 3H - 1,4 - benzodiazepine.

- 9) 4,5-Dehydro derivatives of the compounds formulated in claim 1 in which R³ is absent, wherein R¹ is present and represents a lower-alkyl group, R² and R⁴ are absent and R⁵ is present in the 7-position and represents an amino group.

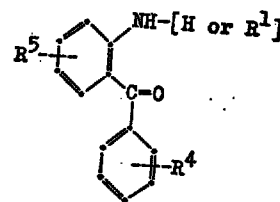
- 10) A process for the manufacture of the substances claimed in claim 1, which process comprises:

- (a) reacting a compound of the general formula

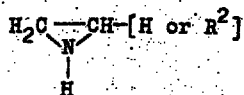


wherein R¹, R², R³ and the broken lines have the significance given in claim 1 and R⁴ and R⁵ represent halogen atoms or trifluoro-methyl, amino, nitro, lower alkylthio, lower alkoxy, lower alkyl or di(lower alkyl)-amino groups, or a 4,5-dehydro-derivative thereof in which R³ is absent, with lithium aluminium hydride, or

- (b) reacting a compound of the general formula

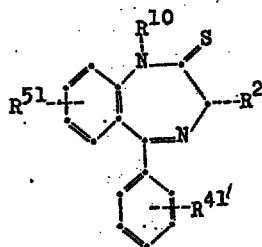


wherein R¹, R⁴, R⁵ and the broken lines have the significance given in claim 1, with a compound of the general formula



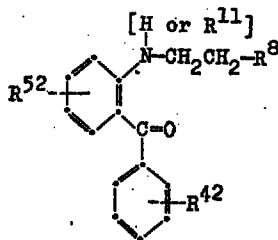
wherein R² has the significance given in claim 1, or

- 5 (c) treating a compound of the general formula



- wherein R² and the broken lines have the significance given in claim 1, R¹⁰ represents lower alkyl or lower alkenyl, R⁴¹ and R⁵¹ represent halogen atoms or trifluoro-methyl, amino, lower alkanoylamino, lower alkoxy, lower alkyl, cyano, carboxy, lower alkoxy-carbonyl or di(lower alkyl)-amino groups, with RANEY-nickel in the presence of a suitable solvent, or

- 15 (d) hydrolysing and cyclising a compound of the formula



- wherein R¹¹ represents a lower alkyl, lower alkenyl or tosyl group and R⁴² and R⁵² represent halogen atoms or lower alkanoylamino, trifluoro-methyl, nitro, lower alkylthio, lower alkoxy, lower alkyl, carboxy, lower alkoxy-carbonyl, cyano or di(lower alkyl)-amino groups, R⁸ is an acylamino group and the broken lines have the significance given in claim 1, either by treatment with an alkaline

agent or by treatment with an acid followed by treatment with a basic agent and, where the compound or derivative obtained by any one of said procedures is basic, converting said compound or derivative into an acid-addition salt.

11) A process as claimed in claim 10 insofar as the product obtained is a compound or derivative in which R¹ or R² is absent, wherein said product is alkylated, alkenylated or alkanoylated in an additional step.

12) A process as claimed in claim 10 insofar as the product obtained is a 1,2-dihydro-compound, wherein said product is reduced in an additional step to form a 1,2,4,5-tetrahydro compound.

13) A process as claimed in claim 10 insofar as the product obtained is a compound or derivative in which the substituent R⁵ (R⁵⁰, R⁵¹ or R⁵²) is absent, wherein said product is subjected to nitration in an additional step.

14) A process as claimed in claim 10 insofar as the product obtained is a compound or derivative in which R⁴ (R⁴⁰ or R⁴¹) or R³ (R³⁰ or R³¹) is an amino group, wherein said product is lower-alkanoylated in an additional step.

15) A process as claimed in claim 10 insofar as the product obtained is a compound or derivative in which R⁴ (R⁴⁰ or R⁴²) or R⁵ (R⁵⁰ or R⁵²) is a nitro group, wherein said product is reduced in an additional step to yield the corresponding amino compound or derivative.

16) A process as claimed in claim 10 insofar as a product containing an amino group is obtained, wherein said product is converted into a corresponding compound in which said amino group is replaced by a cyano group or halogen atom.

17) A process as claimed in claim 10, wherein a starting compound is used in which one or both of the substituents R⁴ (R⁴⁰, R⁴¹ or R⁴²) and R⁵ (R⁵⁰, R⁵¹ or R⁵²) are halogen atoms or trifluoro-methyl, nitro (except in the case of treatment c), lower alkylthio (except in the case of treatment c), cyano (except in the case of treatment d), amino (except in the case of hydrolysis and cyclisation d) or di(lower alkyl)-amino groups.

18) A process as claimed in claim 17, wherein the starting compound is substituted in the 7- (or 5-) and/or 2¹-position.

19) A process as set forth in claim 10 insofar as a trifluoromethyl-substituted product is obtained, wherein said product is converted into a carboxy-substituted or methoxycarbonyl-substituted product in an additional step or additional steps by hydrolysis with a strong acid and cyclisation by treatment with a base and, where the methoxycarbonyl product is required, by methylation of the cyclisation product.

20) A process for the manufacture of the substances claimed in claim 1, substantially as described with reference to the Examples.

21) The substances as set forth in claim 1, when manufactured by the process claimed in any one of claims 10 to 20 inclusive.

- 5 22) A pharmaceutical preparation comprising one or more substances as claimed in claim 1 in admixture with a compatible pharmaceutical carrier.

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