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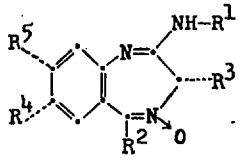
COMPLETE SPECIFICATION

Novel Benzodiazepine 4-Oxides and a process for the Manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel benzodiazepine 4-oxides and to a process for the manufacture thereof.

The novel benzodiazepine 4-oxides provided by the invention are compounds of the general formula:

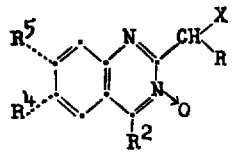


wherein R^1 stands for a hydrogen atom or an alkyl, alkenyl, hydroxy-alkyl or alkoxy-alkyl group, R^2 stands for phenyl or a nitro-phenyl, halogeno-phenyl or alkoxy-phenyl group, R^3 stands for an optional alkyl group and R^4 and R^5 each stands for an optional alkyl or halogeno group (the bonds to the optional groups being denoted by broken lines), and acid addition salts thereof. These substances are useful as sedatives. They may be administered orally or parenterally in the form of the base or a salt thereof with a medicinally acceptable acid in conventional dosage forms such as capsules, tablets, powders or injectables for example. They are also useful for increasing the appetite in animals.

The alkyl groups represented by R^1, R^3, R^4 and R^5 in the foregoing formula may be either straight or branched chain groups; preferably those containing up to seven carbon atoms, e.g., methyl, ethyl, propyl, *iso*propyl, butyl, *iso*butyl and *iso*amyl. The alkenyl groups represented by R^1 may also be straight or branched chain groups; preferably those containing up to seven carbon atoms, e.g. allyl, butenyl and *iso*butenyl. One class of preferred substances comprises those compounds in which R^3 and R^5 are absent, R^2 stands for phenyl and R^4 stands for a halogeno group and acid addition salts thereof, especially those in which R^1 stands for a hydrogen atom and those in which R^1 stands for a lower-alkyl group.

Examples of the acid addition salts provided by the invention are those formed between compounds of the foregoing formula and mineral acids such as the hydrohalic acids, sulphuric acid, nitric acid and phosphoric acid.

According to the process provided by the invention, the substances aforesaid are manufactured by reacting a halide of the general formula:



(wherein R^2, R^4, R^5 and the broken lines have the significance already given, R stands for a hydrogen atom or an alkyl group and X stands for a halogen atom), or a salt thereof, with a compound of the formula $R^1—NH_2$ (wherein R^1 has the significance already given) and, if desired, transforming the product into a salt by treatment with an acid.

The process is carried out preferably at room temperature (i.e. *ca* 20°C) in water or in an inert organic solvent such as a lower aliphatic alcohol, dioxane or tetrahydro-furan. Primary amines of the formula $R^1—NH_2$ which may be used include alkyl amines and alkenyl amines, preferably alkyl and alkenyl amines containing up to seven carbon atoms in their alkyl or alkenyl groups (which may be

[*Price 3s. 6d.*]

Price 4s 6d.

further substituted by hydroxy or alkoxy groups). These primary amines may be, for example, methyl amine, ethyl amine, propyl amine, *iso*propyl amine, allyl amine, ethanol amine, propanol amine, methoxy-ethyl amine and ethoxy-butyl amine.

In order to prepare the preferred group of compounds, the starting materials are 2-(halogeno - methyl) - 4 - phenyl - 6 - halogeno-quinazoline 3-oxides, but 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide is especially preferred.

The halide starting materials generically formulated hereinbefore and their (often unstable) acid addition salts are also novel. These halides and salts thereof are described and claimed in the specification of our copending application for Letters Patent No. 29,235/60 (now serial no: 864,825). As indicated in that specification, they may be prepared by converting an *o*-amino-benzophenone into its oxime with hydroxyl amine, acylating the oxime to give the (α-halogeno-acyl)-*o*-amino-benzophenone oxime (e.g. with an α-halogeno-acyl halide such as chloro-acetyl chloride) and dehydrating the product thus obtained by the action of such acid agents as hydrogen chloride or concentrated sulphuric acid whereby ring closure occurs.

The following examples are illustrative of the process of the invention:

EXAMPLE 1

98 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide hydrochloride were introduced into 600 ml of ice-cold 25% methanolic methyl amine. The mixture was initially cooled to about 30°C and then stirred at room temperature. After 15 hours the reaction product which precipitated was filtered off. The mother-liquor was concentrated *in vacuo* to dryness. The residue was dissolved in methylene chloride, washed with water and dried with sodium sulphate. The methylene chloride solution was concentrated *in vacuo* and the crystalline residue was boiled with a small amount of acetone to dissolve the more soluble impurities. The mixture was then cooled at 5°C for 10 hours and filtered. The crystalline product, 2-(methyl-amino)5-phenyl-7-chloro - 3H - 1,4 - benzodiazepine 4 - oxide, was recrystallized from ethanol forming light yellow plates; m.p. 236°—236.5°C.

A solution of 2-(methyl-amino)-5-phenyl-7-chloro - 3H - 1,4 - benzodiazepine 4 - oxide in an equivalent amount of methanolic hydrochloric acid was diluted with ether and petroleum ether. The precipitated hydrochloride was filtered off and recrystallized from methanol; m.p. 212°—213°C.

EXAMPLE 2

A suspension of 40 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide in 400 ml of 15% ethanolic ammonia was stirred for 5 hours at room temperature. The precipitated 2 - amino - 5 - phenyl - 7 - chloro - 3H-1,4-benzodiazepine 4-oxide was filtered off and washed with water and ether. The product was recrystallized from methanol forming slightly yellowish prisms; m.p. 255°—256°C.

A solution of the base in an equivalent amount of 1-*N* methanolic hydrochloric acid was diluted with ether and petroleum ether. 2 - amino - 5 - phenyl - 7 - chloro - 3H-1,4 - benzodiazepine 4 - oxide hydrochloride precipitated as colourless, water soluble plates; m.p. 245—246°C.

EXAMPLE 3

A suspension of 20 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide in 100 ml of 33% ethanolic ethyl amine was stirred for 14 hours at room temperature. The precipitated reaction product was then filtered off and recrystallized from acetone. The product, 2 - (ethyl - amino) - 5 - phenyl - 7 - chloro-3H - 1,4 - benzodiazepine 4-oxide, formed slightly yellowish prisms; m.p. 231°—233°C.

A solution of the base in an equivalent amount of ethanolic hydrochloric acid was diluted with ether and petroleum ether. 2-(ethyl - amino) - 5 - phenyl - 7 - chloro - 3H-1,4-benzodiazepine 4-oxide hydrochloride precipitated as colourless, water soluble prisms, m.p. 208°—209°C.

EXAMPLE 4

A solution of 15 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide in 60 ml of methanol and 30 ml of butyl amine was left at room temperature for 14 hours. The reaction product which has precipitated was filtered off and the mother liquor was concentrated *in vacuo*. The residue was dissolved in an excess of dilute ice-cold hydrochloric acid. The neutral impurities were extracted with ether and discarded. The mixture was then made alkaline with ice-cold sodium hydroxide solution and the basic products were extracted into ether. The ether solution was concentrated to a small volume and was left for the product to crystallize. The 2-(butyl-amino)-5-phenyl-7-chloro-3H-1,4-benzodiazepine 4-oxide thus obtained was crystallized from acetone as slightly yellow prisms; m.p. 202°—203°C.

A solution of 2-(butyl-amino)-5-phenyl-7-chloro-3H-1,4-benzodiazepine 4-oxide in an equivalent amount of 1-*N* methanolic hydrochloric acid was diluted with acetone, ether and petroleum ether. The precipitated product was recrystallized from *iso*propanol with the addition of acetone and ether. The hydrochloride formed thin colourless plates; m.p. 171°—173°C.

EXAMPLE 5

A solution of 30 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide in a cooled mixture of 120 ml methanol and 60 ml allyl amine was left at room temperature for 24 hours. The precipitated 2-(allyl-amino)-5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide was filtered off. The mother-liquor was concentrated *in vacuo* and the residue was

dissolved in ice-cold 1-*N* hydrochloric acid. Neutral impurities were extracted with ether. The acid aqueous part was made alkaline with the addition of ice-cold sodium hydroxide solution and the basic reaction product was extracted with ether. The ether layer was dried with sodium sulphate, concentrated *in vacuo* and the product crystallized upon the addition of acetone and petroleum ether, yielding additional crystals of 2-(allyl-amino)-5-phenyl-7-chloro-3H-1,4-benzodiazepine 4-oxide. The material was recrystallized from methanol, forming slightly yellowish prisms; m.p. 202°—204°C.

The base obtained as described above was dissolved in an equivalent amount of 1-*N* methanolic hydrochloric acid and the hydrochloride salt was precipitated by the addition of acetone, ether and petroleum ether. The hydrochloride was obtained in the form of colourless plates darkening at 180°C and melting at 221°—227°C (with decomposition).

EXAMPLE 6

A mixture of 10 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide, 40 ml of ethanol amine and 100 ml methanol was stirred at room temperature for 18 hours. The solution was then diluted with ether and petroleum ether and left at 5°C for 16 hours. The precipitated prisms which formed were filtered off and the mother-liquor was concentrated *in vacuo*. The residue was dissolved in an excess of a mixture of ice and 3-*N* hydrochloric acid. The neutral impurities were extracted with ether and discarded. The aqueous part was made alkaline with ice-cold 3-*N* sodium hydroxide solution and extracted with ether. The ether solution containing the basic reaction product, 2-(β-hydroxyethylamino)-5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide, was dried, concentrated *in vacuo* to a small volume and combined with the prisms previously obtained. The product was recrystallized from methanol forming slightly yellowish prisms; m.p. 216°—218°C.

A solution of 2-(β-hydroxy-ethylamino)-5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide in an equivalent amount of 1-*N* methanolic hydrochloric acid was diluted with ether and petroleum ether. The precipitated hydrochloride was filtered off and recrystallized from a mixture of methanol and ether; m.p. 210°—211°C (with decomposition).

EXAMPLE 7

A solution of 12 g of 2-(chloro-methyl)-4-phenyl-6-chloro-quinazoline 3-oxide in 70 ml of warm dioxane was cooled and combined with 30 ml of β-methoxy-ethyl amine containing about 30% water. After standing 3 days at room temperature, the mixture was concentrated *in vacuo* and the residue was dissolved in ice-cold 1-*N* hydrochloric acid. The neutral impurities were extracted with ether. The acidic aqueous portion was cooled, made alkaline with sodium hydroxide solution and the basic reaction product was extracted with ether. The ether layer was dried over sodium sulphate and quickly filtered. The filtrate was partially concentrated *in vacuo* and yielded a crystalline precipitate of the crude reaction product. The product, 2-(β-methoxy-ethylamino) - 5 - phenyl - 7 - chloro - 3H - 1,4-benzodiazepine 4-oxide, was purified by repeated crystallization from acetone, forming yellowish prisms; m.p. 225°—226°C.

The base, 2 - (β - methoxy - ethylamino)-5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide, was dissolved in an equivalent amount of 1-*N* methanolic hydrochloric acid and the crystalline hydrochloride salt was precipitated by the addition of ether; m.p. 207°—209°C.

EXAMPLE 8

A solution of 7 g of 2-(α-bromo-ethyl)-4-phenyl - 6 - chloro - quinazoline 3 - oxide in 30 ml warm dioxane was cooled and added to an ice-cold 20% solution of methyl amine in dioxane. The mixture was left at room temperature for 48 hours and then concentrated to dryness *in vacuo*. Ether was added to the residue and the reaction product was extracted with ice-cold dilute hydrochloric acid. The acid solution was made alkaline with sodium hydroxide solution and the basic reaction product extracted with ether. The ether solution was dried and concentrated *in vacuo*, and the residue was crystallized from acetone. 2-(methyl - amino) - 3 - methyl - 5 - phenyl-7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide was obtained as slightly yellow prisms; m.p. 246°—247°C.

The base was dissolved in an equivalent amount of 1-*N* methanolic hydrochloric acid. 2 - (methyl - amino) - 3 - methyl - 5 - phenyl-7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide hydrochloride was precipitated by the addition of acetone, ether and petroleum ether and recrystallized from methanol by the addition of acetone and ether; m.p. 190°—191°C.

EXAMPLE 9

8 g of 2-(chloro - methyl) - 4 - phenyl - 6,7-dichloro-quinazoline 3-oxide were dissolved with stirring in 135 ml of a 35% solution of methyl amine in methanol. After standing 20 hours at room temperature, the crystalline reaction product was filtered off. The mother-liquor was then concentrated *in vacuo*. The concentrate was dissolved in ice-cold 1-*N* hydrochloric acid and washed with ether. The reaction product was precipitated from the acidic aqueous solution with ice-cold alkali and extracted with ether. The ether solution was concentrated *in vacuo* and the remaining crystals were suspended in methanol and filtered off. The two batches of crude crystalline material, 2-(methyl-amino)-5-phenyl-7,8-dichloro - 3H - 1,4 - benzodiazepine 4-oxide, were recrystallized from methanol, forming yellowish prisms melting at 233°—234°C.

To a suspension of 2-(methyl-amino)-5-

phenyl-7,8 - dichloro - 3H-1,4-benzodiazepine 4-oxide in methanol was added an equivalent amount of methanolic hydrochloric acid. The solution was partly concentrated *in vacuo* and the crystalline hydrochloride was precipitated by the addition of ether and petroleum ether. Upon recrystallization from methanol by the addition of ether and petroleum ether, the colourless hydrochloride melted at 231°—232°C.

EXAMPLE 10

16.4 g of 2-(chloro-methyl)-4-phenyl-6-bromo-quinazoline 3-oxide were stirred at room temperature with 80 ml of a 30% solution of methyl amine in methanol. The precipitated reaction product, 2 - (methyl - amino) - 5-phenyl - 7 - bromo - 3H - 1,4 - benzodiazepine 4-oxide, was filtered off after 24 hours and recrystallized from acetone; m.p. 242°—243°C.

The base was dissolved in an equivalent amount of methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue was crystallized from a mixture of methanol and ether. 2 - (methyl - amino) - 5-phenyl - 7 - bromo - 3H - 1,4 - benzodiazepine 4-oxide hydrochloride was obtained in the form of colourless prisms; m.p. 239°—240°C (with decomposition).

EXAMPLE 11

A suspension of 14 g of 2-(chloro-methyl)-4 - phenyl - 6 - bromo - quinazoline 3-oxide in 400 ml of 15% ethanolic ammonia was stirred at room temperature for 20 hours. The precipitated reaction product was filtered off and recrystallized from methanol. The 2-amino - 5 - phenyl - 7 - bromo - 3H - 1,4-benzodiazepine 4-oxide was obtained in the form of flat white needles, m.p. 261°—262°C.

8.8 g of the base were suspended in 200 ml of methanol and treated with an equivalent amount to 5-*N* methanolic hydrochloric acid. The resulting solution was diluted with ether and petroleum ether. The fine needles which precipitated were filtered off and recrystallized from methanol by the addition of ether and petroleum ether. The 2-amino-5-phenyl-7-bromo - 3H - 1,4 - benzodiazepine 4 - oxide hydrochloride was obtained in the form of fine needles; m.p. 243°—244°C.

EXAMPLE 12

25 g of 2 - (chloro - methyl) - 4 - phenyl-quinazoline 3-oxide were introduced into 200 ml of ice-cold 25% methanolic methyl amine. The mixture was stirred at room temperature for 15 hours and then concentrated *in vacuo*. Ether was added to the residue and the precipitated crystals were filtered off and washed with water and ether. After recrystallization from acetone, the pure 2 - (methyl - amino)-5 - phenyl - 3H - 1,4 - benzodiazepine 4-oxide formed rosettes of colourless needles melting at 190°—191°C.

A solution of 2 - methyl - amino - 5-phenyl - 3H - 1,4 - benzodiazepine 4-oxide in an equivalent amount of 1-*N* methanolic hydrochloric acid was diluted with acetone, ether and petroleum ether. The precipitated hydrochloride was filtered off and recrystallized from the same mixture of solvents. The pure hydrochloride formed colourless prisms melting at 225°—226°C.

EXAMPLE 13

A solution of 15 g of 2-(chloro-methyl)-4-phenyl - 6 - methyl - quinazoline 3-oxide in 50 ml of benzene was added to 150 ml of 35% methanolic methyl amine. The mixture was left at room temperature for 16 hours and then concentrated *in vacuo* to dryness. The residue was dissolved in an excess of dilute ice-cold hydrochloric acid and neutral impurities were extracted with ether and discarded. The mixture was then made alkaline with ice-cold sodium hydroxide solution and the basic reaction product was extracted with ether. The ether solution was dried and concentrated *in vacuo* and the residue was crystallized from acetone with the addition of petroleum ether. The product, 2 - (methyl - amino) - 5 - phenyl-7 - methyl - 3H - 1,4 - benzodiazepine 4-oxide, was recrystallized from acetone, forming slightly yellow prisms melting at 214°—215°C.

The base was dissolved in an equivalent amount of 1-*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a small amount of methanol with the addition of acetone, ether and petroleum ether. The pure hydrochloride of 2 - (methyl - amino) - 5 - phenyl - 7-methyl - 3H - 1,4 - benzodiazepine 4-oxide formed colourless rhombic prisms melting at 224°—225°C.

EXAMPLE 14

A suspension of 10 g of 2-(chloro-methyl)-4-phenyl - 6,7 - dimethyl - quinazoline 3-oxide in 100 ml of 35% methanolic methyl amine was stirred for 16 hours at room temperature. The precipitated 2-methylamino-5-phenyl-7,8-dimethyl - 3H - 1,4 - benzodiazepine 4-oxide was filtered off and recrystallized from acetone, forming slightly yellowish prisms melting at 259°—261°C.

The base was dissolved in an equivalent amount of 1-*N* methanolic hydrochloric acid. The solution was concentrated in vacuo to a small volume and diluted with acetone. The 2 - (methyl - amino) - 5 - phenyl - 7,8-dimethyl - 3H - 1,4 - benzodiazepine 4-oxide hydrochloride which precipitated in colourless prisms was filtered off and washed with acetone and ether; m.p. 230°—231°C.

EXAMPLE 15

15 g of 2 - (chloro-methyl)-4-(4¹-methoxy-phenyl)-quinazoline 3-oxide were introduced with stirring into 150 ml of 35% methanolic methyl amine. Complete solution occurred after 20 minutes. The solution was concentrated *in vacuo* after two hours and water and ether were added to the residue. The precipitated crystals were filtered off. After recrystal-

wherein the reaction is carried out at *ca.* 20°C in water or in an inert organic solvent.

21) A process in accordance with claim 19 or claim 20, wherein the compound of the general formula $R^1—NH_2$ used in the reaction is ammonia or an alkyl or alkenyl amine containing up to seven carbon atoms.

22) A process in accordance with any one of the preceding process claims, wherein the halide used as a starting material is a 2-(halogeno - methyl) - 4 - phenyl - 6 - halogeno-quinazoline 3-oxide or a hydrohalide thereof.

23) A process in accordance with claim 22, wherein the halide used as the starting material is a 2-(halogeno - methyl) - 4 - phenyl - 6-chloro-quinazoline 3-oxide or a hydrochloride thereof.

24) A process in accordance with any one of the preceding process claims, which process comprises reacting 2 - (chloro - methyl) - 4-phenyl - 6 - chloro - quinazoline 3-oxide with methyl amine and, if desired, transforming the product into an acid salt by treatment with an acid.

25) A process for the manufacture of the substances claimed in claim 1 hereof, substantially as described with reference to the examples given.

W. D. WHITAKER,
Patent Agent,
For: F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

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lization from a mixture of ethanol and petroleum ether, the 2 - (methyl - amino) - 5- (4^1 - methoxy - phenyl) - 3H - 1,4 - benzodiazepine 4-oxide formed colourless prisms melting at 251—252°C.

A solution of the above base in an equivalent amount of 1-*N* methanolic hydrochloric acid was concentrated *in vacuo* and the residue crystallized from a small amount of methanol with the addition of acetone and ether. The thus obtained hydrochloride of 2-(methylamino) - 5 - (4^1 - methoxy - phenyl) - 3H-1,4-benzodiazepine 4-oxide formed colourless rosettes of plates melting at 218°—219°C.

EXAMPLE 16

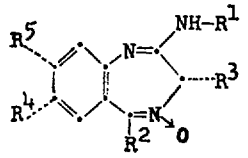
A suspension of 25 g of 2-(chloro-methyl)-4 - (4^1 - chloro - phenyl) - 6,7 - dimethylquinazoline 3-oxide in 250 ml of 30% methanolic methyl amine was stirred at room temperature for 15 hours.

The precipitated 2 - (methyl - amino) - 5- (4^1 - chloro - phenyl) - 7,8 - dimethyl - 3H-1,4 - benzodiazepine 4-oxide was filtered off and recrystallized from methanol; m.p. 258°—259°C.

The base was suspended in a 20-fold amount of methanol and dissolved by the addition of an equivalent amount of 1-*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue was recrystallized from a small amount of water with addition of ethanol, acetone and ether. The 2-(methyl - amino) - 5 - (4^1 - chloro - phenyl)-7,8 - dimethyl - 3H - 1,4 - benzodiazepine 4-oxide hydrochloride formed colourless needles melting at 247°—248°C.

WHAT WE CLAIM IS:—

1) Compounds of the general formula:



wherein R^1 stands for a hydrogen atom or an alkyl, alkenyl, hydroxy-alkyl or alkoxy-alkyl group, R^2 stands for phenyl or a nitro-phenyl, halogeno-phenyl or alkoxy-phenyl group, R^3 stands for an optional alkyl group and R^4 and R^5 each stand for an optional alkyl or halogeno group (the bonds to the optional groups being denoted by broken lines), and acid addition salts thereof.

2) Compounds as claimed in claim 1 and acid addition salts thereof, wherein the alkyl or alkenyl groups represented by R^1 and the alkyl groups by R^3, R^4 and R^5 are groups which contain up to seven carbon atoms.

3) 2 - (methyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

4) 2 - Amino - 5 - phenyl - 7 - chloro-3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

5) 2 - (ethyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

6) 2 - (butyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

7) 2 - (allyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

8) 2 - (β - hydroxy - ethylamino) - 5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

9) 2 - (β - methoxy - ethylamino) - 5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

10) 2 - (methyl - amino) - 3 - methyl - 5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

11) 2 - (methyl - amino) - 5 - phenyl - 7,8-dichloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

12) 2 - (methyl - amino) - 5 - phenyl - 7-bromo - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

13) 2 - amino - 5 - phenyl - 7 - bromo-3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

14) 2 - methyl - amino - 5 - phenyl - 3H-1,4 - benzodiazepine and its hydrochloride.

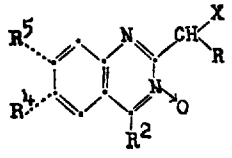
15) 2 - (methyl - amino) - 5 - phenyl - 7-methyl - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

16) 2 - (methyl - amino) - 5 - phenyl - 7,8-dimethyl - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

17) 2-(methyl - amino) - 5 - (4^1 - methoxy-phenyl) - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

18) 2 - (methyl - amino) - 5 - (4^1 - chlorophenyl) - 7,8 - dimethyl - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

19) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises reacting a halide of the general formula



(wherein R^2, R^4, R^5 and the broken lines have the significance given in claim 1, R stands for a hydrogen atom or an alkyl group and X stands for a halogen atom), or a salt thereof, with a compound of the general formula $R^1—NH_2$ (where R^1 has the significance given in claim 1) and, if desired, transforming the product into a salt by treatment with an acid.

20) A process in accordance with claim 19,

lization from a mixture of ethanol and petroleum ether, the 2 - (methyl - amino) - 5-(4^1 - methoxy - phenyl) - 3H - 1,4 - benzodiazepine 4-oxide formed colourless prisms melting at 251—252°C.

A solution of the above base in an equivalent amount of 1-*N* methanolic hydrochloric acid was concentrated *in vacuo* and the residue crystallized from a small amount of methanol with the addition of acetone and ether. The thus obtained hydrochloride of 2-(methylamino) - 5 - (4^1 - methoxy - phenyl) - 3H-1,4-benzodiazepine 4-oxide formed colourless rosettes of plates melting at 218°—219°C.

EXAMPLE 16

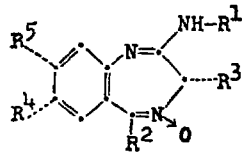
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The precipitated 2 - (methyl - amino) - 5-(4^1 - chloro - phenyl) - 7,8 - dimethyl - 3H-1,4 - benzodiazepine 4-oxide was filtered off and recrystallized from methanol; m.p. 258°—259°C.

The base was suspended in a 20-fold amount of methanol and dissolved by the addition of an equivalent amount of 1-*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue was recrystallized from a small amount of water with addition of ethanol, acetone and ether. The 2-(methyl - amino) - 5 - (4^1 - chloro - phenyl)-7,8 - dimethyl - 3H - 1,4 - benzodiazepine 4-oxide hydrochloride formed colourless needles melting at 247°—248°C.

WHAT WE CLAIM IS:—

1) Compounds of the general formula:



wherein R^1 stands for a hydrogen atom or an alkyl, alkenyl, hydroxy-alkyl or alkoxy-alkyl group, R^2 stands for phenyl or a nitro-phenyl, halogeno-phenyl or alkoxy-phenyl group, R^3 stands for an optional alkyl group and R^4 and R^5 each stand for an optional alkyl or halogeno group (the bonds to the optional groups being denoted by broken lines), and acid addition salts thereof.

2) Compounds as claimed in claim 1 and acid addition salts thereof, wherein the alkyl or alkenyl groups represented by R^1 and the alkyl groups by R^3, R^4 and R^5 are groups which contain up to seven carbon atoms.

3) 2 - (methyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

4) 2 - Amino - 5 - phenyl - 7 - chloro-3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

5) 2 - (ethyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

6) 2 - (butyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

7) 2 - (allyl - amino) - 5 - phenyl - 7-chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

8) 2 - (β - hydroxy - ethylamino) - 5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

9) 2 - (β - methoxy - ethylamino) - 5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

10) 2 - (methyl - amino) - 3 - methyl - 5-phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

11) 2 - (methyl - amino) - 5 - phenyl - 7,8-dichloro - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

12) 2 - (methyl - amino) - 5 - phenyl - 7-bromo - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

13) 2 - amino - 5 - phenyl - 7 - bromo-3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

14) 2 - methyl - amino - 5 - phenyl - 3H-1,4 - benzodiazepine and its hydrochloride.

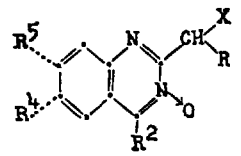
15) 2 - (methyl - amino) - 5 - phenyl - 7-methyl - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

16) 2 - (methyl - amino) - 5 - phenyl - 7,8-dimethyl - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

17) 2-(methyl - amino) - 5 - (4^1 - methoxy-phenyl) - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

18) 2 - (methyl - amino) - 5 - (4^1 - chlorophenyl) - 7,8 - dimethyl - 3H - 1,4 - benzodiazepine 4-oxide and its hydrochloride.

19) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises reacting a halide of the general formula



(wherein R^2, R^4, R^5 and the broken lines have the significance given in claim 1, R stands for a hydrogen atom or an alkyl group and X stands for a halogen atom), or a salt thereof, with a compound of the general formula R^1—NH_2 (where R^1 has the significance given in claim 1) and, if desired, transforming the product into a salt by treatment with an acid.

20) A process in accordance with claim 19,