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vonBebenburg et al.

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[45] **Nov. 18, 1975**

[54] **NEW 6-AZA-1,4 -BENZODIAZEPINE**

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[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.**..... **260/239.3 B;** 260/296 H; 424/263

[51] **Int. Cl.**[2]..... **C07D 471/04**

[58] **Field of Search** ..... 260/239.3 B

[56] **References Cited**

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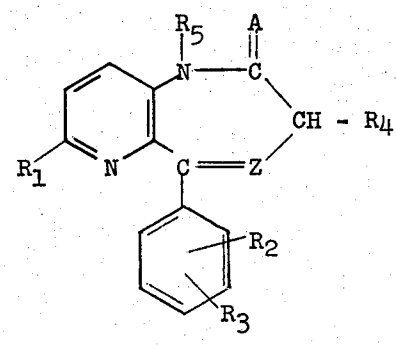
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

There are prepared compounds of the formula:



where:

R_1 is a halogen;

R_2 and R_3 are hydrogen, halogen, trifluoromethyl, nitro, nitrile, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms;

R_4 is hydrogen, hydroxy, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, carbamoyloxy ($H_2NCO—O—$) or carbamoxyloxy substituted with (1) an alkyl group of 1 to 6 carbon atoms, (2) alkenyl of 2 to 6 carbon atoms, or (3) cycloalkyl of 3 to 6 carbon atoms;

Z is nitrogen or the group ≡ NO;

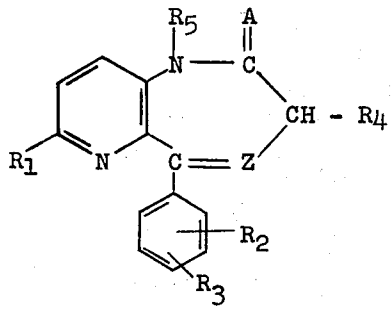
R_5 is carbamoyl, thiocarbamoyl or carbamoyl or thiocarbamoyl substituted with (1) alkyl of 1 to 6 carbon atoms, (2) alkenyl of 2 to 6 carbon atoms, or (3) cycloalkyl of 3 to 6 carbon atoms; and

A is oxygen, sulfur or =N-R where R is hydrogen or alkyl of 1 to 6 carbon atoms and the group $—C(=A)—CHR_4$ can also be in the tautomeric form $—(C(AR_4)—CH—$ and pharmaceutically acceptable salts thereof. The compounds have psychosedative, anxiolytic and antiphlogistic activity.

10 Claims, No Drawings

NEW 6-AZA-1,4 -BENZODIAZEPINE

The invention is directed to new 6-aza-1H-1,4-benzodiazepines and 6-aza-1,2-dihydro-3H-1,4-benzodiazepines of the formula:



I

wherein:

R_1 is halogen;

R_2 and R_3 are the same or different and are hydrogen, halogen, trifluoromethyl, nitro, nitrile, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms;

R_4 is hydrogen, hydroxy, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, carbamoyloxy ($H_2NCO—O—$) or carbamoyloxy substituted with (1) an alkyl group of 1 to 6 carbon atoms, (2) alkenyl of 2 to 6 carbon atoms, or (3) cycloalkyl of 3 to 6 carbon atoms;

Z is nitrogen or the group $\equiv$ NO;

R_5 is carbamoyl, thiocarbamoyl or carbamoyl or thiocarbamoyl substituted with (1) alkyl of 1 to 6 carbon atoms, (2) alkenyl of 2 to 6 carbon atoms, or (3) cycloalkyl of 3 to 6 carbon atoms; and

A is oxygen, sulfur or —N—R where R is hydrogen or alkyl of 1 to 6 carbon atoms and the group —C(=A)—CHR_4 can also be in the tautomeric form —C(AR_4)=CH— and pharmaceutically acceptable salts thereof.

In the compounds of formula I the halogen atoms can have an atomic weight of 9 to 80, i.e., they can be chlorine, fluorine or bromine, preferably chlorine. As the above-named alkyl, alkenyl and alkoxy groups there are employed alkyl and alkoxy groups of 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, and alkenyl groups of 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms. The carbamoyl or thiocarbamoyl groups as well as the carbamoyloxy groups can be mono or di substituted on the nitrogen by lower alkyl, preferably of 1 to 4 carbon atoms, or lower alkenyl, preferably of 1 to 4 carbon atoms. Examples of alkyl, alkenyl and alkoxy groups which can be present include methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, hexyl, isobutyl, methoxy ethoxy, isopropoxy, butoxy, isobutoxy, tert.-butoxy, amyloxy, hexoxy, vinyl, allyl, methallyl, crotyl, propoxy, sec. butyl. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl and cyclohexyl.

In addition to the compounds mentioned in the working examples other compounds within the present invention include:

1-carbamoyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-thiocarbamoyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-ethylamino-thiocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-methylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-methylamino-carbonyl-5-(o-trifluoromethyl phenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-dimethylamino-carbonyl-5-(o-methylphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-diethylamino carbonyl-5-(p-methylphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-isopropylamino-carbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-butylaminocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-hexylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-cyclopropylamino-carbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-cyclopentylaminocarbonyl-5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-diallylaminocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-methallylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-vinylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-crotylamino-carbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone(2);

1-ethylaminocarbonyl-5-phenyl-6-aza-7-bromo-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-propylamino-carbonyl-5-phenyl-6-aza-7-fluoro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-t-butylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-ethylaminocarbonyl-5-(o-bromo-phenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-allylamino-carbonyl-5-(o-cyanophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-ethylaminocarbonyl-5-(m-nitrophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-ethylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazethiopinone-(2);

1-allylaminocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazethiopinone-(2);

1-methylaminocarbonyl-5-phenyl-6-aza-7-fluoro-1,2-dihydro-3H-1,4-benzodiazethiopinone-(2);

1-ethylaminocarbonyl-2-methylamino-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepine;

1-allylamino-carbonyl-2-ethylamino-5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepine;

1-propylaminocarbonyl-2-butylamino-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepine;

1-isopropylaminocarbonyl-2-hexylamino-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepine;

1-ethylamino-carbonyl-3-carbamoyloxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

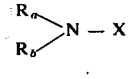
1-allylaminocarbonyl-3-methylcarbamoyloxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);

1-ethylaminocarbonyl-3-allylcarbamoyloxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylamino-carbonyl-3-hexylcarbamoyloxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-3-cyclohexylcarbamoyloxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-5-(o,p-dimethylphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-allylaminocarbonyl-5-(o-methoxyphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-methylaminocarbonyl-5-(p-ethoxyphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-5-(o-butylphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-allylaminocarbonyl-5-(o-butoxyphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-5-(o-hexylphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-5(p-t-butylphenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2)-4-oxide;
1-allylamino-carbonyl-3-methyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-methylaminocarbonyl-3-methoxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-3-butoxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-3-butyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-3-hexyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-allylaminocarbonyl-3-isopropyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-ethylaminocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2)-4-oxide;
1-ethylaminocarbonyl-5-(2',5'-dichlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-allylaminocarbonyl-3-hydroxy-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2);
1-butylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinthione-(2).

The compounds of the invention have valuable pharmacodynamic properties. For example, they have psychosedative and especially anxiolytic (tranquilizing) properties. Furthermore, an antiphlogistic action is also present.

The compounds of formula I can be prepared by methods which are known in themselves such as:

a. reacting a compound of formula I wherein R_5 is hydrogen and the other symbols are as defined above with a compounds of the formula



II

where X is the group —COCl, the group —COBr, the group —COOR' where R' is a lower alkyl group (1 to 6 carbon atoms), phenyl or benzyl, the group —CONHY where Y is NO, NO_2 or an acyl group, e.g., acetyl, propionyl or benzoyl, the group CON_3 (Azidocarbonyl), the group CO or the group CS. When X is CO or CS one of the substituents R_a or R_b is eliminated and there is a double bond between the N-atom and X. R_a and R_b are hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 1 to 6 carbon atoms or one of R_a or R_b is cycloalkyl of 3 to 6 carbon atoms, or

b. in a compound of formula I one or more of the symbols R4, R_5, A and Z can be changed to give a compound of corresponding meaning.

In a given case, after carrying out process (a) or (b), wherein the compound obtained has OH as R_4, this hydroxy group can be alkylated or can be acylated with a compound of formula II wherein X, R_a and R_b have the meanings set forth above.

Process (a) can take place for example in solvents or suspension media, especially dioxane, tetrahydrofurane, toluene, benzene, alpha-naphthalene, dimethyl formamide, dimethyl sulfoxide, glacial acetic acid, water, chloroform or methylene chloride at temperatures between 0° and 200° C., especially 20° to 150° C. In a given case it is suitable to add basic materials, for example organic bases such as pyridine, trialkyl amines such as trimethyl amine and triethyl amine, dimethyl aniline, N-ethyl piperidine or inorganic basic materials such as alkali hydroxides, e.g., sodium hydroxide and potassium hydroxide, alkali carbonates, e.g., sodium carbonate and potassium carbonate, alkali bicarbonates, e.g., sodium bicarbonate and potassium bicarbonate, etc. It is also possible that is using the compounds of formula II which contain a halogen atom that the corresponding hydrohalide escapes as a gas during the reaction or in a given case forms a salt with the end product. In case Y is an acyl residue it is preferably a lower aliphatic acyl group, e.g., an alkanoyl group, for example, acetyl, or a substituted aliphatic acyl group, for example, phenyl acetyl.

Compounds of formula I in which R_4 is an alkyl group or an alkoxy group can be produced from compounds wherein R_4 is hydrogen or OH respectively by alkylation. The alkylation takes place, for examples, by reaction with esters of the formula HalR'', $SO_2(OR'')$ or $ArSO_2OR''$, where Hal is a halogen atom, especially Cl, Br or I, Ar is an aromatic radical (especially in a given case a phenyl or naphthyl radical with one or more lower alkyl radicals, e.g., methyl or ethyl) and R'' is an alkyl group with 1 to 6 carbon atoms. Thus, there can be used methyl chloride, ethyl bromide, propyl iodide, hexyl chloride, dimethyl sulfate, diethyl sulfate, methyl-p-toluene sulfonate, butyl-p-toluene sulfonate. the alkylation reaction takes place, in a given case, with addition of customary acid binding agents such as alkali carbonates, e.g., sodium carbonate and potassium carbonate, pyridine or other customary tertiary amines, e.g., triethyl amine and N,N-dimethyl aniline, at temperatures between 0° and 150° C. in inert solvents such as alcohols, e.g., methyl alcohol, ethyl alcohol and isopropyl alcohol, dioxane, dimethyl formamide, dimethyl sulfoxide, aromatic hydrocarbons such as benzene, toluene and acetone as well as mixtures of such solvents.

For the alkylation with alkyl halides (for example iodides) in the presence of NaH there has been found favorable, for example, a mixture of toluene and a little dimethyl formamide (0.1 to 5%, for example 0.5%). In the alkylation it can also be provided that the compound of formula I in which R_4 is H or OH can first be converted to an alkali compound if it is treated with an

alkali metal, alkali hydride or alkali amide (especially sodium or sodium compounds such as sodium hydride and sodamide) in an inert solvent such as dioxane, dimethyl formamide, benzene or toluene at temperatures between 0° and 150° C. and then the alkylating agent added.

According to process (b) azabenzodiazepines of formula I can be reacted further in suitable manner. The group A in a compound of formula I can be exchanged in various ways. Thus in case A is oxygen, this atom can be replaced by sulfur with the aid of phosphorus pentasulfide. This reaction takes place in inert solvents such as benzene, toluene, dioxane, pyridine or chlorohydrocarbons, e.g., chloroform, at temperatures between 0° and 150° C. Compounds in which A is oxygen or sulfur (cyclic amides) can be reacted again in polar media with ammonia or alkylamines with 1 to 6 carbon atoms, e.g., methyl amine, ethyl amine, butyl amine, hexyl amine, t-butylamine, where compounds of formula I are formed in which A is imino or alkylimino. These reactions are carried out for example in polar solvents such as methanol, ethanol or excess amine, at temperatures between 0° and 150° C.

For example, compounds can be obtained in which R_4 is a hydroxy group by oxidation. For this purpose compounds of formula I in which R_4 is a hydrogen atom are reacted in inert solvents such as acetic acid, ethyl acetate or acetone with hydrogen peroxide, peracetic acid or other customary organic peroxides. The temperature is preferably between −10° and +100° C.

Compounds of formula I wherein R_4 is a carbamoyloxy group (especially an alkyl, alkenyl or cycloalkyl substituted carbamoyloxy group) can also be obtained by reacting a compound of formula I in which R_4 is H and Z is $\rightarrow$ NO in an inert solvent such as dioxane, tetrahydrofurane, dimethyl formamide and dimethyl sulfoxide with a compound of formula II. Thereby a rearrangement occurs according to which the oxygen atom attached to the nitrogen forms a hydroxyl group on the adjacent carbon atom. This rearrangement is carried out at temperatures between 0° and 150° C., especially 0° to 100° C. An excess of component II can also function as solvent.

Compounds of formula I wherein Z is a nitrogen atom can be converted into the corresponding N-oxide. The reagents and conditions are analogous to those of the hydroxylation of R_4. The temperatures generally are somewhat lower, preferably between 0° and 50° C.

In compounds of formula I where Z is the group $\equiv$NO the oxygen atom can be removed by catalytic hydrogenation, or by chemical deoxygenation. As catalysts for the catalytic hydrogenation there are suitable, for example, the customary metallic hydrogenation catalysts, especially noble metal catalysts (palladium/activated carbon, platinum) or Raney-nickel; as solvents there are preferably employed lower alcohols, e.g., methanol, ethanol or isopropanol. The temperatures are between 0° and 200° C., preferably between 0° and 100° C. In a given case the process can be carried out at pressures up to 50 atmospheres absolute. For chemical deoxygenation there are preferably used phosphorus trichloride or dimethyl sulfoxide in inert solvents such as dioxane, benzene or toluene at temperatures between 0° and 150°C., preferably 0° to 100° C.

In compounds of formula I wherein R_5 is a thiocarbamoyl group, the sulfur atom can be replaced by oxygen. This change of the sulfur atom, for example, can take place by treatment of the thiourea at a temperature between 0° and about 250° C., preferably 0° to 100° C. or also 0° to 50° C. with 1 to 5 moles of potassium ferricyanide, iron (III) chloride, potassium permanganate, potassium chloride, potassium chlorate, potassium hypochlorite, heavy metal oxides such as lead oxide, mercuric oxide, or peroxides such as hydrogen peroxide, sodium peroxide, peracetic acid and similar acting materials, suitably in the presence of a solvent. As solvents there can be used water, methanol, ethanol, propanol, tetrahydrofurane, dioxane, dimethyl formamide, acetone or mixtures of these agents (especially with water).

Furthermore, compounds of formula I wherein R_4 is the OH group can be reacted with compounds of formula II under the conditions of process (a), or compounds wherein R_4 is H or the OH group can be converted by alkylation as stated above into compounds wherein R_4 is an alkyl radical or an alkoxy radical. For example, the alkylation takes place by reaction with esters of the formula HalR'', $SO_2(OR'')$ or $ArSO_2OR''$, wherein Hal is a halogen atom, especially Cl, Br or I, Ar is an aromatic radical (especially in a given case a phenyl or naphthyl radical substituted by one or more lower alkyl groups) and R'' is an alkyl group with 1 to 6 carbon atoms. Examples are p-toluenesulfonic acid alkyl esters, e.g., methyl-p-toluenesulfonate, ethyl-p-toluenesulfonate, lower dialkyl sulfates, e.g., dimethyl sulfate and diethyl sulfate and the like. The alkylation reaction takes place, in a given case, with addition of customary acid binding agents such as alkali carbonate, e.g., sodium carbonate and potassium carbonate, pyridine or other customary tertiary amines at temperatures between 0° and 150° C. in inert solvents such as alcohols, e.g., methyl alcohol, ethyl alcohol or propyl alcohol, dioxane, dimethyl formamide, dimethyl sulfoxide, aromatic hydrocarbons such as benzene or toluene or acetone as well as mixtures of such solvents.

For the alkylation with alkyl halides (for example, iodides) in the presence of NaH it has been found favorable to react in a mixture of toluene and a little dimethyl formamide (0.1 to 5%, for example 0.5%).

In the alkylation it can also be provided that the compound of formula I in which R_4 is H or OH can first be converted to an alkali compound if it is treated with an alkali metal, alkali hydride or alkali amide (especially sodium or sodium compounds such as sodium hydride and sodamide) in an inert solvent such as dioxane, dimethyl formamide, benzene or toluene at temperatures between 0° and 150° C. and then the alkylating agent added.

Basic compounds of Formula I can be converted into their salts by conventional methods. As anions for these salts there can be employed the known and therapeutically usable (pharmacologically acceptable) acid residues. For example, there can be used acids such as sulfuric acid, phosphoric acid, hydrohalic acids, e.g., hydrochloric acid or hydrobromic acid, ethylenediamine tetraacetic acid, sulfamic acid, benzene sulfonic acid, p-toluene sulfonic acid, camphor sulfonic acid, methane sulfonic acid, guarazulene sulfonic acid, maleic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, citric acid, ascorbic acid, glycolic acid, salicylic acid, acetic acid, propionic acid, gluconic acid, benzoic acid, acetamidoacetic acid, hydroxyethane sulfonic acid, malonic acid.

The free bases can be produced again from the salts of the compounds in customary manner, for example, by treatment of a solution in an organic medium, such

as alcohols (e.g., methanol, ethanol or isopropanol) with soda or soda lye (caustic soda solution).

Those compounds of formula I which contain asymmetric carbon atoms and as a rule result as racemates, can be split into the optically active isomers in known manner with the help of an optically active acid. However, it is also possible to employ from the beginning an optically active starting material whereby a correspondingly optically active or diastereomer form is obtained as the end product.

The compounds of the invention are suitable for the production of pharmaceutical compositions. The pharmaceutical compositions or medicaments can contain one or more of the compounds of the invention or mixtures of the same with other pharmaceutically active materials. For the production of pharmaceutical preparations there can be used the customary pharmaceutical carriers and assistants. The medicines can be employed enterally, parenterally, orally or perlingually. For example, dispensing can taken place in the form of tablets, capsules, pills, dragees, plugs, salves, jellies, cremes, powders, liquids, dusts or aerosols. As liquids there can be used, for example, oily or aqueous solutions or suspensions, emulsions, injectable aqueous and oily solutions or suspensions.

For example, there can be made and used in the invention compounds of formula I where the symbols R_1 to R_5 as well as A and Z have the following meaning:

R_1 is chlorine;

R_2 is chlorine, fluorine, CF_3, or alkyl with 1 to 3 carbon atoms, e.g., methyl, ethyl, propyl or isopropyl, preferably methyl, preferably in the ortho or para position, and hydrogen. The preferred substituents are hydrogen or fluorine or chlorine in the ortho position;

R_3 is hydrogen, fluorine or chlorine with the o-position being preferred;

R_4 is hydrogen or an alkyl group with 1 to 6 carbon atoms, e.g., methyl, ethyl, isopropyl, isobutyl, sec. butyl, t-butyl, amyl or hexyl, especially 1 to 3 carbon atoms, or a hydroxy group or the alkylcarbamoyloxy group with 1 to 4 carbon atoms, especially hydrogen;

R_5 is ethylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl or dipropylaminocarbonyl or allylaminocarbonyl;

A is especially oxygen and also is sulfur or imino or alkylimino with 1 to 6 carbon atoms, for example, methylimino, ethylimino, propylimino, butylimino, hexylimino; and

Z is nitrogen.

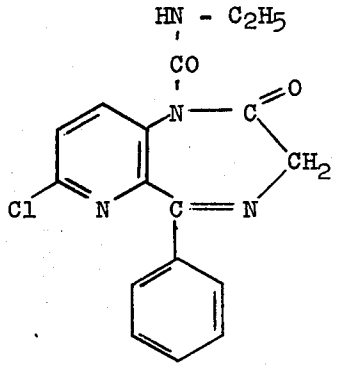
Especially favorable activity is possessed by compounds of formula I, where R_1 is chlorine, R_2 and R_3 are the same or different and are hydrogen, fluorine or chlorine, preferably in the ortho position, A is an oxygen atom and Z is a nitrogen atom, R_4 is hydrogen or hydroxyl and R_5 is an ethylaminocarbonyl or an allylaminocarbonyl.

The starting compounds used in process (a) can be prepared for example according to the process of Austrian Application A 10604/71 or von Bebenburg et al U.S. application Ser. No. 313,542, filed Dec. 8, 1972 or in analogous manner to those processes. The entire disclosure of the von Bebenburg et al U.S. Application is hereby incorporated by reference. These starting compounds are claimed as new compounds in said von Bebenburg et al application.

Unless otherwise indicated, all percentages are by weight.

EXAMPLE 1:

1-ethylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

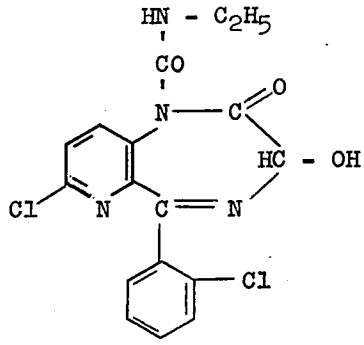


A mixture of 13.5 grams (0.05 mole) of 5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2) (prepared as described in Example 1 of von Bebenburg application Ser. No. 313,542), 200 ml of tetrahydrofurane and 40 ml of ethyl isocyanate were heated at reflux for 8 hours with stirring, then at intervals of 4 hours there were added two further amounts of 10 ml of ethyl isocyanate and the mixture boiled further. The solution was evaporated in a vacuum and the syrupy residue recrystallized from a little n-propanol.

Yield 6.5 grams; M.P. 127° C.

EXAMPLE 2:

1-ethylaminocarbonyl-3-hydroxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

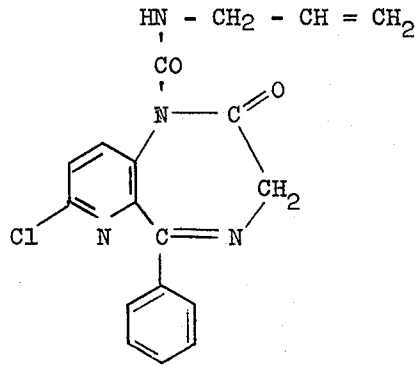


A mixture of 13 grams of 3-hydroxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); (prepared as described in Example 13 of the von Bebenburg application 313,542); 100 ml of tetrahydrofurane and 40 ml of ethyl isocyanate were boiled for one hour under reflux in a nitrogen atmosphere. The mixture was evaporated in a vacuum, the solid residue was recrystallized from n-propanol.

Yield 11.5 grams; M.P. 259° to 263° C. (with decomposition).

EXAMPLE 3:

1-allylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

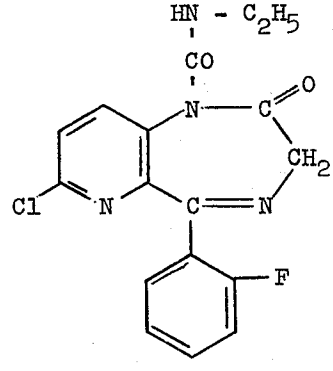


A mixture of 13.5 grams of 5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2), 100 ml of tetrahydrofurane and 40 ml. of allyl isocyanate were heated under reflux in a nitrogen atmosphere for 4 hours, then another 10 ml of allylisocyanate were added and boiling continued for another 30 minutes. After the cooling, the desired compound slowly crystallized out. It was filtered off with suction and recrystallized from ethanol.

Yield 8.2 grams; M.P. 137° to 139° C.

EXAMPLE 4:

1-ethylaminocarbonyl-5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

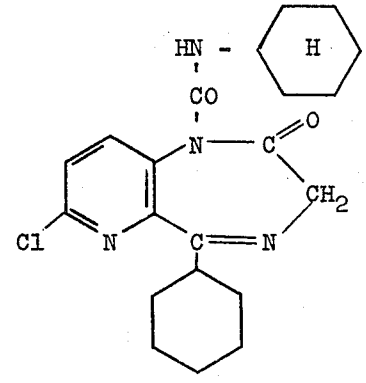


A mixture of 20 grams of 5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2) (prepared as described in example 10 of the von Bebenburg application Ser. No. 313,542), 50 ml of ethyl isocyanate and 100 ml of tetrahydrofurane were boiled under reflux for 8 hours with stirring, then 10 ml more of ethyl isocyanate were added and boiling continued for 4 hours. The compound crystallized out upon cooling.

Yield 9.5 grams; M.P. 119° to 121°C.

EXAMPLE 5:

1-(cyclohexylaminocarbonyl)-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

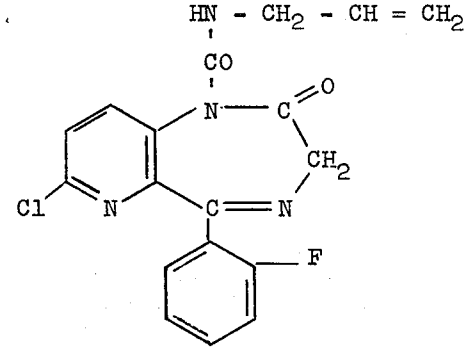


A mixture of 20 grams of 5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2), 40 ml of cyclohexyl isocyanate and 100 ml of tetrahydrofurane were heated at reflux with stirring for 6 hours, then 60 ml of tetrahydrofurane were distilled off and the mixture heated at reflux for another 5 hours. After cooling, the reaction product crystallized out. It was recrystallized from 50 ml of dimethyl formamide and 150 ml of methanol.

M.P. 252° C.

EXAMPLE 6:

1-(allylaminocarbonyl)-5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

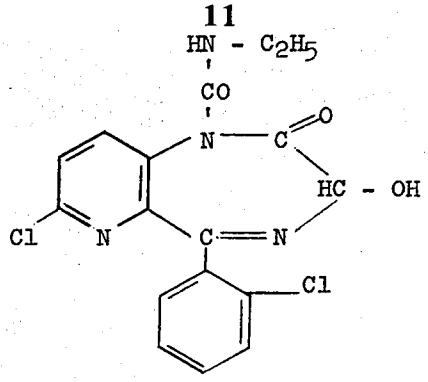


A mixture of 20 grams of 5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2), 40 ml of allyl isocyanate and 100 ml of tetrahydrofurane were heated at reflux for 7 hours. Upon cooling, the reaction product crystallized out. It was washed with ethanol.

M.P. 138°–140° C.

EXAMPLE 7:

1-ethylaminocarbonyl-3-hydroxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2):

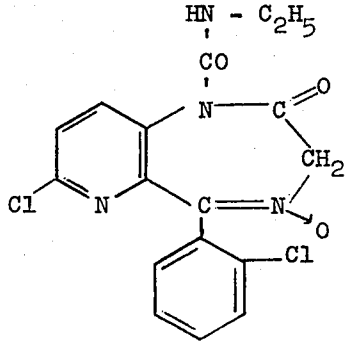


A mixture of 13 grams of 3-hydroxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2), 40 ml of ethyl isocyanate and 100 ml of tetrahydrofurane were heated at reflux with stirring and in a nitrogen atomsphere for 1 hour. The mixture was carefully concentrated in a vacuum and the residue recrystallized from n-propanol.

M.P. 259°–263° C.

EXAMPLE 8:

1-ethylaminocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2)-4-oxide:



20 grams of 5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2)-4-oxide (made in a manner analogous to that used in von Bebenburg application Ser. No. 313,542, Example 3 for preparing 5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2)4-oxide but starting from 2-o-chlorobenzoyl-3-amino-6-chloropyridine) were heated at reflux in 80 ml of ethyl isocyanate with stirring for 8 hours. The cooled mixture was treated 4 times with 100 ml of gasoline, decanted off from the precipitating syrup, whereupon after the last addition of gasoline the desired substance slowly crystallized out.

M.P. 129° C.

The compounds of the invention are suited for the production of pharmaceutical compositions and preparations. The pharmaceutical compositions or drugs contain as the active material one or several of the compounds of the invention, in a given case in admixture with other pharmacologically or pharmaceutically effective materials. The production of the medicine can

take place with the use of known and customary pharmaceutical assistants, carriers and diluents.

Such carriers and assistants as set forth for example are those recommended in the following literature as adjuvants for pharmacy, cosmetic and related fields such as in Ullmann's Encyklopadie der technischer Chemie, Vol. 4 (1953), pages 1 to 39; Journal of Pharmaceutical Sciences, Vol. 52 (1963), pages 918 et seq.; H. v. Czetsch-Lindenwald, Hilfstoffe fur Pharmazie und angrenzende Gebiete; Pharm. Ind. Vol. 2 (1961), pages 72 et seq.; Dr. H. P. Fiedler, Lexicon der Hilfstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete, Cantor Kg. Aulendorf i. Württ, 1971.

Examples of such materials include gelatin, natural sugars such as sucrose or lactose, lecithin, pectin, starch (for example corn starch), tylose, talc, lycopodium, silica (for example colloidal silica), glucose, cellulose, cellulose derivatives for example cellulose ethers in which the cellulose hydroxyl groups are partially etherified with lower aliphatic alcohols and/or lower saturated oxyalcohols, (for example, methyl hydroxypropyl cellulose, methyl cellulose, hydroxyethyl cellulose) stearates, e.g., methylstearate, and glyceryl stearate, magnesium and calcium salts of fatty acids with 12 to 22 carbon atoms, especially saturated acids (for example calcium stearate, calcium laurate, magnesium oleates, calcium palmitate, calcium behenate and magnesium stearate), emulsifiers, oils and fats, especially of plant origin (for example, peanut oil, castor oil, olive oil, sesame oil, cottonseed oil, corn oil, mono-, di- and triglycerides of saturated fatty acids ($C_{12}H_{24}O_2$ to $C_{18}H_{36}O_2$ and their mixtures, e.g., glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl trilaurate), pharmaceutically compatible mono- or polyvalent alcohols and polyglycols such as glycerine, mannitol, sorbitol, pentaerythritol, ethyl alcohol, diethylene glycol, triethylene glycol, ethylene glycol, propylene glycol dipropylene glycol, polyethylene glycol 400 and other polyethylene glycols, as well as derivatives of such alcohols and polyglycols, esters of saturated and unsaturated fatty acids (2 to 22 carbon atoms, especially 10 to 18 carbon atoms), with mono- (1 to 20 carbon atoms alkanols) or polyhydric alcohols such as glycols, glycerine, diethylene glycol, pentaerythritol, sorbitol, mannitol, ethyl alcohol, butyl alcohol, octadecyl alcohol, etc., e.g., glyceryl stearate, glyceryl palmitate, glycol distearate, glycol dilaurate, glycol diacetate, monoacetin, triacetin, glyceryl oleate, ethylene glycol sterate; such esters of polyvalent alcohols can in a given case also be etherified, benzyl benzoate, dioxolane, glycerine formal, glycol furfural, dimethyl acetamide, lactamide, lactates, e.g., ethyl lactate, ethyl carbonate, silicones (especially middle viscosity dimethyl polysiloxane) and the like.

For the production of solutions there can be used water or physiologically compatible organic solvents, as for example, ethanol, 1,2-propylene glycol, polyglycols, e.g., diethylene glycol, triethylene glycol and dipropylene glycol and their derivatives, dimethyl sulfoxide, fatty alcohols, e.g., stearyl alcohol, cetyl alcohol, lauryl alcohol and oleyl alcohol, triglycerides, e.g., glyceryl acetate, partial esters of glycerine, e.g., monoacetic diacetin, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitate, paraffins and the like.

In the production of the preparations there can be used known and conventional solvent aids. As solvent aids there can be used, for example, polyoxyethylated

fats, e.g., polyoxyethylated oleo triglyceride, linolized oleotriglyceride. Examples of oleotriglycerides are olive oil, peanut oil, castor oil, sesame oil, cottonseed oil, corn oil (see also Dr. H. P. Fiedler, "lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete", 1971, pages 191 to 195.

Polyoxyethylated means that the materials in question contain polyoxyethylene chains whose degree of polymerization is generally between 2 and 40 and especially between 10 and 20. Such materials can be obtained for example by reaction of the corresponding glyceride with ethylene oxide (for example 40 moles of ethylene oxide per mole of glyceride).

Furthermore, there can be added preservatives, stabilizers, buffers, taste correctives, antioxidants and complex formers (for example ethylenediamine tetraacetic acid) and the like. In a given case for stabilization of the active molecule the pH is adjusted to about 3 to 7 with physiologically compatible acids or buffers. Generally, there is preferred as neutral as possible to weak acid (to pH 5) pH value. As antioxidants there can be used for example sodium meta bisulfite, ascorbic acid, gallic acid, alkyl gallates, e.g., methyl gallate and ethyl gallate, butyl hydroxyanisole, nordihydroguararetic acid, tocopherols such as tocopherol and synergists (materials which bind heavy metals by complex formation, for example, lecithin, ascorbic acid, phosphoric acid). The addition of synergists increases considerably the antioxidant activity of tocopherol. As preservatives there can be used for example sorbic acid, p-hydroxybenzoic acid esters (for example, lower alkyl esters such as the methyl ester and the ethyl ester benzoic acid), sodium benzoate, trichloroisobutyl alcohol, phenol cresol, benzethonium chloride and formalin derivatives).

The pharmacological and galenical treatment of the compounds of the invention takes place according to the usual standard methods. For example, the active material or materials and assistants or carriers are well mixed by stirring or homogenization (for example by means of a colloid mill or ball mill), wherein the operation is generally carried out at temperatures between 20° and 80° C., preferably 20° to 50° C.

The drugs can be used for example orally, parenterally, rectally, vaginally, perlingually or locally.

The lowest effective dosage in the above-mentioned animal experiments is for example 5 mg/kg body weight orally, 0.5 mg/kg body weight intravenously and 1 mg/kg sublinqually.

As general dosage ranges there can be used 5 to 100 mg/kg body weight orally, 0.5 to 10 mg/kg body weight intravenously and 1–20 mg/kg sublinqually.

The compounds of the invention in the spasm test of Tedeschi (mouse) as well as in the motility test on the mouse in the circular cage of F. Heim show a good anxiolytic (tranquilizing) and calming activity.

This activity is comparable to the activity of the known medicine Diazepoxid.

The lowest effective dosage in the above-mentioned animal experiments for example is 0.5 mg/kg body weight orally, 0.1 mg/kg sublinqually and 0.05 mg/kg intravenously.

As a general dosage range there can be used, for example, 0.5 to 10 mg/kg body weight orally, 0.1 to 2 mg/kg sublingually and 0.05 to 1 mg/kg intravenously.

The compounds of the invention are useful in treating anxiety, stress and restlessness conditions, vegatative dystony, nervousness, irritability, moodiness, footlight fever (of actors), weather feelings, behavior and adaptability problems of children, functional cardiovascular, gastrointestinal and respiratory complaints. They are also useful in menstrual and climatic disturbances, aiding before operation and in assiting birth.

The pharmaceutical preparations generally contain between 1 and 10% of the active component (or components) of the invention.

The compounds can be delivered in the form of tablets, capsules, pills, dragees, suppositories, salves, gels, creams, powders, liquids, dusts or aerosols. As liquids there can be used oily or aqueous solutions or suspensions, emulsions. The preferred forms of use are as tablets which contain between 1 and 50 mg of active material or solutions which contain between 0.1 and 5% of active material.

In individual doses the amount of active component of the invention can be used for example in an amount of:

a. in oral dispensation between 15 and 50 mg,
b. in parenteral dispensation (for example, intravenously, intramuscularly) between 0.1 and 5 mg,
c. in inhalation dispensation (solutions or aerosols) between 0.5 and 10 mg,
d. in rectal or vaginal dispensation between 10 and 50 mg.

(The dosages in each case are based on the free base).

For example, there is recommended the use of 1 to 3 tablets containing 1 to 50 mg of active ingredient 3 times daily or for example intravenously the injection 1 to 3 times daily of a 1 to 2 ml ampoule containing 0.1 to 10 mg of active substance. In oral preparations the minimum daily dosage for example is 3 mg; the maximum daily dosage should not be over 200 mg.

In the treatment of dogs and cats the oral individual dosage in general is between 0.5 and 50 mg/kg body weight; the parenteral individual dosage is between about 0.1 and 10 mg/kg body weight. In the treatment of horses and cattle, the individual dosage orally is generally between 5 and 100 mg/kg; the parenteral individual dosage is between 1 and 20 mg/kg body weight.

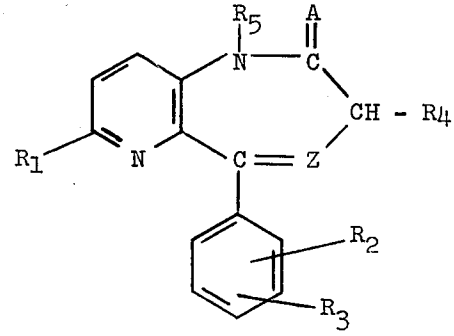
The acute toxicity of the compounds of the invention in the mouse (expressed by the LD_{50} mg/kg method of Miller and Tainter, *Proc. Soc. Exper. Biol. and Med.*, *Vol.* 57 (1944), pages 261, et seq.) in oral application is between 500 mg/kg and 10,000 mg/kg (or above 8000 mg/kg).

The drugs can be used in human medicine, in veterinary medicine, e.g., to treat cats, dogs, horses, sheep, cattle goats and pigs or in agriculture. The drugs can be used alone or in admixture with other pharmacologically active materials.

The salts can also be used as curing agents for melamineformaldehyde resins.

What is claimed is:

1. A 6-aza-1H-1,4-benzodiazepine or 6-aza-1,2-dihydro-3H-1,4-benzodiazepine of the formula:



wherein:

R_1 is a halogen;

R_2 and R_3 are hydrogen, halogen, trifluoromethyl, nitro, nitrile, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms;

R_4 is hydrogen, hydroxy, alkyl of 1 to 6 carbon atoms; or alkoxy of 1 to 6 carbon atoms;

Z is nitrogen or the group ≡ NO;

R_5 is carbamoyl, thiocarbamoyl or carbamoyl or thiocarbamoyl substituted with (1) alkyl of 1 to 6 carbon atoms, (2) alkenyl of 2 to 6 carbon atoms, or (3) cycloalkyl of 3 to 6 carbon atoms; and

A is oxygen and pharmaceutically acceptable salts thereof.

2. A compound according to claim **1,** wherein any halogen present has an atomic weight of 9 to 80.

3. A compound according to claim **2** wherein R_1 is chlorine.

4. A compound according to claim **3,** wherein R_2 is hydrogen, chlorine, fluorine, bromine or trifluoromethyl, R_3 is hydrogen, R_4 is hydrogen or hydroxyl, R_5 is carbamoyl or carbamoyl substituted with (1) alkyl of 1 to 6 carbon atoms, (2) alkenyl of 3 to 6 carbon atoms of (3) cycloalkyl of 3 to 6 carbon atoms.

5. A compound according to claim **4** wherein R_5 is or carbamoyl orcarbamoyl substituted with alkyl of 1 to 4 carbon atoms, alkenyl of 3 to 4 carbon atoms or cyclohexyl.

6. A compound according to claim **5** wherein R_2 is hydrogen, chlorine or fluorine, R_5 is carbamoyl mono substituted with alkyl of 1 to 3 carbon atoms, allyl or cyclohexyl.

7. A compound according to claim **6** wherein the R_2 substituent is in the ortho position.

8. A compound according to claim **3** wherein R_2 is hydrogen, fluorine, CF_3 or alkyl of 1 to 3 carbon atoms, R_3 is hydrogen, fluorine or chlorine, R_4 is hydrogen, alkyl of 1 to 6 carbon atoms or hydroxy, R_5 is carbamoyl mono substituted with alkyl of 1 to 3 carbon atoms, disubstituted with alkyl of 1 to 3 carbon atoms or mono substituted with allyl, and Z is nitrogen.

9. A compound according to claim **8** wherein R_2 is hydrogen, fluorine, chlorine or methyl, R_3 is hydrogen, R_4 is hydrogen, alkyl of 1 to 3 carbon atoms or hydroxy, R_5 is ethylaminocarbonyl, dimethylaminocarbonyl, dipropylaminocarbonyl or allylaminocarbonyl.

10. A compound according to claim **3** which is (a) -ethylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); (b) 1-ethylaminocarbonyl-3-hydroxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodaizepinone-(2); (c) 1-allylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); (d) 1-ethylaminocarbonyl-5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); (3) 1-cyclohexylaminocarbonyl-5-phenyl-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); (f) 1-allyl-aminocarbonyl-5-(o-fluorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); (g) 1-ethylaminocarbonyl-3-hydroxy-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-benzodiazepinone-(2); or (h) 1-ethylaminocarbonyl-5-(o-chlorophenyl)-6-aza-7-chloro-1,2-dihydro-3H-1,4-diazepinone-(2)-4-oxide.

* * * * *