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3-AMINOALKYL-1,3-BENZODIAZEPIN-2-ONES

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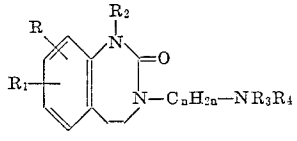
U.S. Cl. 260—239.3 10 Claims

ABSTRACT OF THE DISCLOSURE

The preparation of substituted 3-aminoalkyl-1,3-benzodiazepin-2-ones is described. These compounds can be prepared for example, by ring closure of a substituted N-(O-aminophenethyl-N',N'-dialkylalkylenediamine with N,N'-carbonyldiimidazole, phosgene or the like. The substituted 3-aminoalkyl-1,3-benzodiazepin-2-ones are useful for their antidepressant, hypnotic and muscle relaxant properties.

This invention relates to new organic compounds. More particularly, it relates to 3-aminoalkyl-1,3-benzodiazepin-2-ones and methods of preparing the same.

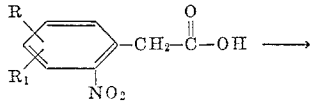
The novel compounds of the present invention have the following structure:



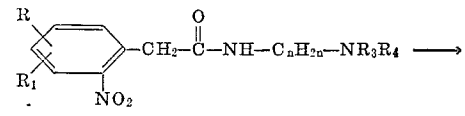
wherein R and R_1 are selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, and trifluoromethyl; R_2 is selected from the group consisting of hydrogen and lower alkyl; n is an integer 2, 3 or 4; and R_3 and R_4 selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aralkyl, (lower cycloalkyl)methyl, and when NR_3R_4 is taken together, 1-pyrrolidinyl, lower alkyl-1-pyrrolidinyl, piperidino, lower alkylpiperidino, 4-phenylpiperidino, 4-halophenylpiperidino, morpholino, lower alkylmorpholino, hexamethyleneimino, 1-piperazinyl, 4-lower alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-phenyl-1-piperazinyl, 4-(lower alkoxyphenyl) - 1-piperazinyl, 4-trifluoromethylphenyl-1-piperazinyl, 4-(lower alkylphenyl)-1-piperazinyl, 4-halophenyl - 1 - piperazinyl, 3,6-dihydro-4-phenyl-1(2H)-pyridyl, 4-alkylphenyl-3,6-dihydro-1(2H)-pyridyl, 3,6-dihydro-4-halophenyl-1(2H)-pyridyl, and azabicyclo-[3.2.2] nonan-3-yl; and acid addition salts thereof.

The compounds of the present invention may be solids or liquids at room temperature as their free bases. As such, they are relatively insoluble in water but are soluble in or miscible with most organic solvents such as, for example, lower alkyl alcohols, esters, acetone, chloroform and the like. These compounds form acid addition salts with strong acids such as hydrochloric acid, sulfuric acid, perchloric and the like. These salts are, in general, soluble in water, methanol, ethanol, etc., but relatively insoluble in benzene, ether, petroleum-ether and the like.

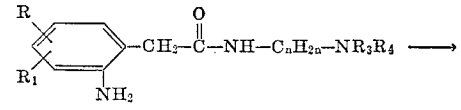
The compounds of this invention may be prepared by the following method which has been found most desirable.



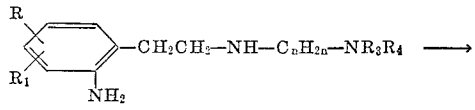
(A)



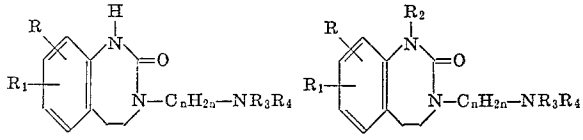
(B)



(C)



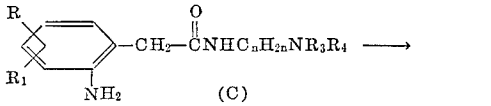
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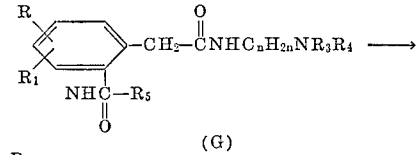
(E) (F)

wherein R, R_1, R_2, R_3, R_4, and n are as defined hereinbefore. When (A) is converted to an acid chloride, an anhydride, an ester or an acylimidazole and then reacted with an aminoalkylamine, (B) is obtained. The nitro group in (B) can be converted to an amino group (C) by one of the usual literature procedures, i.e., catalytically, stannous chloride, calcium chloride in ethanol and the like. The amide group in (C) is reduced by such reagents as lithium aluminum hydride or diborane, and compound (D) results. When (D) is reacted with such reagents as N,N'-carbonyl diimidazole, phosgene and the like, (E) results. If desired, (E) can be converted to (F) by alkylation, preferably in the presence of a condensing agent such as sodium, sodium hydride, or sodamide.

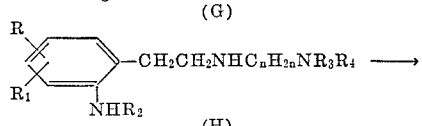
An alkyl group may be introduced at the 1-position at an earlier stage, for example, as described below.



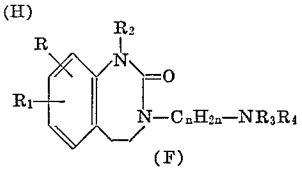
(C)



(G)



(H)

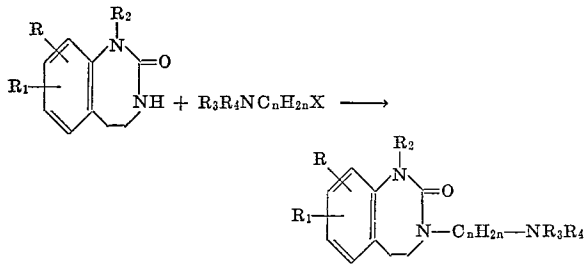


(F)

wherein R, R_1, R_2, R_3, R_4 and n are as defined above and R_5 is an H or lower alkyl group.

In this procedure, (C) is acylated by known literature procedures to (G) and the product is reduced, for example, by lithium aluminum hydride or diborane, to the triamine (H). Cyclization by such agents as N,N'-carbonyldiimidazole, phosgene, ethyl chloroformate and the like results in the desired product (F).

A further method of preparing compounds of this invention is by the alkylation of a 1,3-benzodiazepine-2-one which contains a hydrogen atom in the 3-position.



wherein R, R_1, R_2, R_3, R_4 and *n* are as previously defined and X is a halogen or arylsulfonyloxy group. Suitable solvents for this reaction are benzene, toluene, ethanol, tetrahydrofuran and the like. An acid acceptor such as excess amine or sodium carbonate is desirable and a temperature within the range of 25–175° C. is preferred.

The compounds of this invention are physiologically active in the central nervous system. Some of the compounds such as 3-(2-dimethylaminoethyl)-8-isopropyl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one have antidepressant activity, while others such as 3-(2-dimethylaminoethyl) - 1,3,4,5 - tetrahydro - 1,3 - benzodiazepin - 2 - one show CNS depressant activity.

The antidepressant properties of the compounds prepared by the process of the present invention are determined by measuring their ability to counteract a depression induced in animals by the administration of tetrabenazine hexamate. Graded doses of the active compounds of this invention are administered to groups of mice, and this is followed by administering a dose of tetrabenazine which is known to markedly depress the exploratory behavior of normal mice. The antidepressant treated groups show normal exploratory behavior, while the control groups, and groups treated with an ineffective antidepressant agent, do not show this normal exploratory behavior, but show the well known profound depression induced by tetrabenazine. The results from several dose levels are used to establish effective dose ranges. The anti-depressant compounds prepared by the process of this invention show their desirable properties by this procedure at dose levels which produce little or no untoward side effects.

The CNS depressant properties, such as hypnotic and muscle relaxant type activity is indicated by several procedures. For example, a test which indicates hypnotic and/or muscle relaxant type activity is represented by the following rod walking test. Groups of 6 mice each are tested for their ability to walk across a horizontal rod in a normal manner after receiving graded interperitoneal doses of a test compound. A median effective dose (RWD) is estimated.

A test which indicates tranquilizing activity is represented by a measure of the reduction in motor activity. One-half this dose is given to a group of 5 mice and a 5 minute count of motor activity is recorded (actophotometer). Counts of <250 are considered to indicate a specific reduction (more than two standard deviations) of activity at a dose causing only minimal impairment of neurological function as measured by rod walking ability. Compounds that appeared to reduce motor activity (<250 count) are administered to additional groups of 5 mice at graded doses and tested similarly. The dose (MDD) which causes a 50% reduction of motor activity (a count of 250) is estimated.

As a test for toxicity or margin of safety, the compounds that specifically reduce motor activity are given to 10 mice at a dose of 10× (MDD). The compounds that did not reduce motor activity are given to 10 mice at a dose of 4× (RWD). If more than 50% of the mice die within 24 hours, the compound is rejected for reasons of toxicity or low margin of safety. If <50% of the mice die, the compound is considered for further study.

The compounds of the present invention for use as tranquilizers or antidepressants can be incorporated in various pharmaceutical forms such as tablets, capsules, pills and so forth, for immediate or sustained release, by combining with suitable carriers. The daily dose may vary from 10 mg. to 1000 mg. They may be in the form of dosage units for single therapeutic dose or in small units for multiple dosages or in larger units for division into single doses. Obviously, in addition to the therapeutic compound there may be present excipients, binders, fillers and other therapeutically inert ingredients necessary in the formulation of the desired pharmaceutical preparation.

The following specific examples illustrate the preparation of representative benzodiazepin-2-ones and thiones of the present invention. Parts are by weight unless otherwise indicated.

EXAMPLE 1

Preparation of 3-(2-dimethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

A solution of 8.5 parts of N,N'-carbonyldiimidazole in 70 parts of tetrahydrofuran is added to a solution of 9.0 parts of o-nitrophenylacetic acid in 30 parts of tetrahydrofuran and the mixture is stirred for 30 minutes. A solution of 4.8 parts of N,N-dimethylethylenediamine in 20 parts of tetrahydrofuran is added and the mixture is stirred at 25° C. for 90 minutes and then at reflux temperature for 30 minutes. The reaction mixture is concentrated to remove the solvent and the residue is warmed with 50 parts of warm water and extracted four times with benzene. The benzene layers are combined, washed with a little water and concentrated. The residue crystallizes and is washed onto a filter with ether. The yield of N - (2 - dimethylaminoethyl) - 2 - (o - nitrophenyl)acetamide, melting point 76–78° C., is 64%.

A mixture of 10 parts of N-(2-dimethylaminoethyl)-2-(o-nitrophenyl)acetamide (prepared above), 40 parts of 1 N hydrochloric acid, 160 parts of ethanol and 1 part of 10% palladium-on-carbon catalyst is shaken in a Parr hydrogenator under about 3 atmospheres of hydrogen pressure for 1 hour. The catalyst is filtered off and the mother liquor is concentrated to remove the solvent. The residue is stirred with 30 parts of water and 10 parts of 5 N sodium hydroxide and the mixture is extracted with benzene. The benzene extracts are concentrated and 6.8 parts of pink crystals, melting point 93–95° C., are obtained.

The above material, N-(2-dimethylaminoethyl)-2-(o-aminophenyl)acetamide, is dissolved in 50 parts of tetrahydrofuran and added dropwise to 90 parts by volume of a cooled solution of 1 molar borane in tetrahydrofuran. The mixture is left at room temperature for 20 hours and then heated at reflux temperature for one hour. The mixture is cooled and 25 parts of 5 N hydrochloric acid are carefully added. The tetrahydrofuran is distilled off and 15 parts of sodium hydroxide are carefully added to the remaining reaction mixture. This mixture is extracted with benzene and the benzene layer is washed with water and then concentrated. The N-(o-aminophenethyl)-N',N'-dimethylethylenedamine is obtained as a viscous oil.

A solution of 5.2 parts of the above oil in 50 parts of benzene is cooled and a solution of 4.8 parts of N,N'-carbonyldiimidazole in 50 parts of tetrahydrofuran is added. The solution is allowed to stand at room temperature for 20 hours, heated on the steam bath for 2 hours, and concentrated to remove the solvent. The residue is diluted with 40 parts of water and the product is extracted into benzene. The benzene layer is washed with a little water and concentrated. The residue is triturated with a little ether and filtered and the crystalline product is recrystallized from ethyl acetate. The 3-(2-dimethylaminoethyl)-

1,3,4,5-tetrahydro-2H-1,3-benzodiazepin - 2 - one melts at 114–116° C.

When the above compound is dissolved in benzene and treated with alcoholic hydrogen chloride, the hydrochloride salt precipitates. This product melts at 231–233° C. after recrystallization from ethanol. This compound has (CNS) depressant properties.

EXAMPLE 2

Preparation of 3-(2-pyrrolidinoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one hydrochloride

When the sequence of reactions described in Example 1 is carried out, starting with o-nitrophenyl acetic acid and 1-(2-aminoethyl)pyrrolidine, the above compound, melting point 225–227° C., is obtained. This compound has CNS depressant properties. The above hydrochloride is dissolved in water, sodium hydroxide added and the base compound extracted with benzene.

EXAMPLE 3

Preparation of 3-(2-dimethylaminoethyl)-8-isopropyl-1,3,4,5 - tetrahydro-2H-1,3-benzodiazepin - 2 - one hydrochloride

When 4-isopropyl-2-nitrophenylacetic acid is substituted for o-nitrophenylacetic acid in the procedure of Example 1, the above compound, melting point 215–217° C. is obtained. This compound is active as an anti-depressant. The above hydrochloride is dissolved in water, sodium hydroxide added and the base compound extracted with benzene.

EXAMPLE 4

Preparation of 8-chloro-3-(2-dimethylaminoethyl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

A mixture of 3.9 parts of 2-(4-chloro-2-nitrophenyl)-N-(2-dimethylaminoethyl)acetamide, 2.1 parts of iron powder, 3.2 parts of 5 N hydrochloric acid, and 7.0 parts of 70% ethanol is heated, under nitrogen, at reflux temperature for 45 minutes. The reaction mixture is cooled, diluted with 15 parts of 50% ethanol and filtered. The precipitate is washed with 15 parts of 50% ethanol. The mother liquors are diluted with 50 parts of water and concentrated until the ethanol is removed. The mixture is filtered to remove some insoluble material and the filtrate is treated with 5 parts of 5 N sodium hydroxide and extracted with benzene. The benzene layer is washed with water, dried over magnesium sulfate and concentrated. The crystalline residue is triturated with ether and filtered. The 2 - (2-amino - 4 - chlorophenyl)-N-(2-dimethylaminoethyl)acetamide melts at 89–90° C.

A solution of 2.6 parts of 2-(2-amino-4-chlorophenyl)-N-(2-dimethylaminoethyl)acetamide in 20 parts of tetrahydrofuran is added dropwise, with stirring and under nitrogen, to 30 parts of 1 molar borane in tetrahydrofuran. The mixture is stirred for 30 minutes, left overnight at room temperature and then heated at reflux temperature for one hour. The mixture is cooled and 10 parts of 5 N hydrochloric acid is carefully added. The tetrahydrofuran is distilled off and 6 parts of sodium hydroxide pellets are carefully added. The mixture is extracted with benzene and the benzene layer is washed with water, dried over magnesium sulfate and concentrated. The N-[2-(2-amino-4 - chlorophenyl)ethyl] - N',N' - dimethylethylenediamine is obtained as an oil in nearly quantitative yield.

A solution of 2.4 parts of N-[2-(2-amino-4-chlorophenyl)ethyl]-N,N'-dimethylethylenediamine in 20 parts of tetrahydrofuran is cooled and 1.9 parts of 92% N',N'-carbonyldiimidazole in 30 parts of tetrahydrofuran are added. The solution is left at room temperature for 3 days and then heated on the steam bath for 4 hours. The mixture is concentrated to remove the solvent, warmed with 50 parts of water and filtered. The product, 8-chloro-3-(2-dimethylaminoethyl) - 1,3,4,5 - tetrahydro - 2H - 1,3 - benzodiazepin-2-one melts at 148–150° C. The hydrochloride salt melts at 256–258° C.

EXAMPLE 5

Preparation of 6-chloro-3-(2-dimethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When 2-(6-chloro-2-nitrophenyl)-N-(2-dimethylaminoethyl)acetamide is substituted for 2 - (4 - chloro - 2 - nitrophenyl)-N-(2-dimethylaminoethyl)acetamide in the procedure of Example 4, the above compound, melting point 173–175° C. is obtained.

EXAMPLE 6

Preparation of 8-chloro-3-(2-pyrrolidinoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained when 2-(4-chloro-2-nitrophenyl)-N-(2 - pyrrolidinoethyl)acetamide is substituted for 2 - (4 - chloro - 2 - nitrophenyl) - N - (2 - dimethylaminoethyl)acetamide in the procedure of Example 4.

EXAMPLE 7

Preparation of 8-bromo - 3 - (2-dimethylaminoethyl)-6-methyl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

If 2 - (4 - bromo - 6 - methyl - 2 - nitrophenyl) - N - (2-dimethylaminoethyl)acetamide is substituted for 2-(4-chloro - 2 - nitrophenyl) - N - (2 - dimethylaminoethyl) acetamide in the procedure of Example 4, the above compound is obtained.

EXAMPLE 8

Preparation of 6,8-dichloro-3-(2-dimethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When 2 - (4,6 - dichloro - 2 - nitrophenyl) - N - (2-dimethylaminoethyl)acetamide is substituted for 2-(4-chloro - 2 - nitrophenyl) - N - (2 - dimethylaminoethyl) acetamide in the procedure of Example 4, the above compound is obtained.

EXAMPLE 9

Preparation of 8-fluoro-3-(3-morpholinopropyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained when 2-(4-fluoro-2-nitrophenyl)-N-(3-morpholinopropyl)acetamide is substituted for 2-(4-chloro-2-nitrophenyl)-N-(2-dimethylaminoethyl)acetamide in the procedure of Example 4.

EXAMPLE 10

Preparation of 3-(2-piperidinoethyl)-1,3,4,5-tetrahydro-8-trifluoromethyl-2H-1,3-benzodiazepin-2-one

The above compound is obtained when 2-nitro-4-trifluoromethylphenylacetic acid is substituted for o-nitrophenylacetic acid and 1-(2-aminoethyl)piperidine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1.

EXAMPLE 11

Preparation of 3-(4-dimethylaminobutyl)-8-methoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained when o-nitrophenyl acetic acid is replaced by 4-methoxy-2-nitrophenylacetic acid and N,N-dimethylethylenediamine is replaced by 4-dimethylaminobutylamine in the procedure of Example 1.

EXAMPLE 12

Preparation of 3-(2-dimethylaminoethyl)-8-methyl-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

This compound is obtained when 4-methyl-2-nitrophenylacetic acid is used in place of o-nitrophenylacetic acid in the procedure of Example 1.

EXAMPLE 13

Preparation of 1-ethyl-3-(2-dimethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

If N - [o - (ethylamino)phenethyl] - N,N' - dimethylethylenediamine is treated with N,N'-carbonyldiimidazole

by the procedure of Example 1, this compound is obtained.

EXAMPLE 14

Preparation of 3-(2-benzylmethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained if N-(o-aminophenethyl)-N' - benzyl - N' - methylethylenediamine is treated with N,N'-carbonyl diimidazole as described in Example 1.

EXAMPLE 15

Preparation of 3-(2-methylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

A mixture of 10 parts of 3-(2-benzylmethylaminoethyl) - 1,3,4,5 - tetrahydro - 1,3 - benzodiazepin - 2 one, 150 parts of ethanol and 1 part of 10% palladium-on-carbon catalyst is shaken in a Parr hydrogenator under about 45 pounds of hydrogen pressure until reduction is complete. The catalyst is filtered off and the mother liquor is concentrated to recover the 3-(2-methylaminoethyl) - 1,3,4,5 - tetrahydro - 1,3 - benzodiazepin - 2-one.

EXAMPLE 16

Preparation of 3-(2-methylcyclohexylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

This compound is obtained when N-methyl-N-cyclohexylethylenediamine is substituted for N,N-dimethylenediamine in the procedure of Example 1.

EXAMPLE 17

Preparation of 3 - [2 - methyl(cyclopropylmethyl)aminoethyl] 1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When N - methyl - N - (cyclopropylmethyl)ethylenediamine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1, this compound is obtained.

EXAMPLE 18

Preparation of 3[2-(4-methylpiperidino)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

If 1-(2-aminoethyl)-4-methylpiperidine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1, this compound is obtained.

EXAMPLE 19

Preparation of 3-[2-(3-methyl-1-pyrrolidinyl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

This compound is obtained when 1-(2-aminoethyl)-3-methylpyrrolidine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1.

EXAMPLE 20

Preparation of 3-[2-(2,6-dimethylmorpholino)ethyl] 1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

If 4-(2-aminoethyl)-2,6-dimethylmorpholine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1, this compound is obtained.

EXAMPLE 21

Preparation of 3-[2-hexamethyleneiminoethyl] 1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When 1-(2-aminoethyl)hexamethyleneimine is used in place of N,N-dimethylethylenediamine in the procedure of Example 1, this compound is obtained.

EXAMPLE 22

Preparation of 3-[2-(azabicyclo[3.2.2]nonan-3-yl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained when the N,N-dimethylethylenediamine is replaced by 3-(2-aminoethyl) azabicyclo[3.2.2]-nonane in the procedure of Example 1.

EXAMPLE 23

Preparation of 3-[2-(4-phenylpiperidino)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

If 1-(2-aminoethyl)-4-phenylpiperidine is used in place of N,N-dimethylethylenediamine, the above compound is obtained.

EXAMPLE 24

Preparation of 3-[2-(4-ethyl-1-piperazinyl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When 1-(2-aminoethyl)-4-ethylpiperazine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1, the above compound is prepared.

EXAMPLE 25

Preparation of 3-[2-(4-benzyl-1-piperazinyl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained when 1-benzyl-4-[2-(o-aminophenethylamino)ethyl]piperazine is treated with N,N'-carbonyldiimidazole as described in Example 1.

EXAMPLE 26

Preparation of 3[2-(1-piperazinyl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When 3 - [2 - (4 - benzyl - 1 - piperazinyl)ethyl] - 1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one is reduced by the procedure of Example 15, the above compound is obtained.

EXAMPLE 27

Preparation of 3-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

If 1-(2-aminoethyl)-4-phenylpiperazine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1, this compound is obtained.

EXAMPLE 28

Preparation of 3 - [2 - (4 - p - chlorophenyl - 1 - piperazinyl)ethyl] - 1,3,4,5 - tetrahydro-2H - 1,3-benzodiazepin-2-one

This compound is obtained when 1-(p-chlorophenyl)-4-[2-(o-aminophenethylamino)ethyl]piperazine is treated with N,N'-carbonyldiimidazole as described in Example 1.

EXAMPLE 29

Preparation of 3-[2-(4-p-ethylphenyl-1-piperazinyl)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

When 1-(2-aminoethyl)-4-p-ethylphenylpiperazine is substituted for N,N-dimethylethylenediamine in the procedure of Example 1, this compound is obtained.

EXAMPLE 30

Preparation of 3-[2-(4-m-methoxyphenyl)-1-piperazinyl) ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

The above compound is obtained when 1-(2-aminoethyl)-4-m-methoxyphenylpiperazine is substituted for N,N-dimethylenediamine in the procedure of Example 1.

EXAMPLE 31

Preparation of 3-[2-(4-m-trifluoromethylphenyl)-1-piperazinyl)ethyl] - 1,3,4,5 - tetrahydro-2H-1,3-benzodiazepin-2-one

If 1-(2 - aminoethyl)-4-m-trifluoromethylphenylpiperazine is used in place of N,N-dimethylethylenediamine in the procedure of Example 1, the above compound is obtained.

EXAMPLE 32

Preparation of 3-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridyl)ethyl - 1,3,4,5 - tetrahydro-2H-1,3-benzodiazepin-2-one

This compound is obtained when 1-[2-(o-aminophen-

ethylamino)ethyl]-4-phenyl-1,2,3,5 - tetrahydropyridine is treated with N,N'-carbonyldiimidazole as described in Example 1.

EXAMPLE 33

Preparation of 3-[2-(3,6 - dihydro-4-m-tolyl-1(2H)-pyridyl)ethyl] - 1,3,4,5 - tetrahydro-2H-1,3-benzodiazepin-2-one

When 1-[2-(o-aminophenethylamino)ethyl]-4-m-tolyl-1,2,5,6-tetrahydropyridine and N,N'-carbonyldiimidazole are reacted as described in Example 1, the above compound is obtained.

EXAMPLE 34

Preparation of 3 - [2 - (4 - p-chlorophenyl-3,6-dihydro-1(2H) - pyridyl)ethyl] - 1,3,4,5 - tetrahydro - 2H-1,3-benzodiazepin-2-one

If 4 - p - chlorophenyl-1-[2-(o-aminophenethylamino) ethyl]-1,2,5,6-tetrahydropyridine is treated with N,N'-carbonyldiimidazole as described in Example 1, the above compound is prepared.

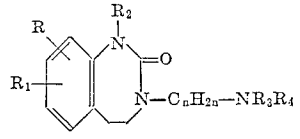
EXAMPLE 35

Preparation of 3-[2-(4-p-chlorophenylpiperidino)ethyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

This compound is obtained when 4-(p-chlorophenyl)-1-[2-(o-aminophenethylamino)ethyl]piperidine is treated with N,N'-carbonyldiimidazole as described in Example 1.

I claim:

1. A benzodiazepin-2-one of the formula:



wherein R and R_1 are selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy and trifluoromethyl; R_2 is selected from the group consisting of hydrogen and lower alkyl; *n* is an integer 2, 3 or 4; and R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, cyclohexyl, benzyl, cyclopropylmethyl and when NR_3R_4 is taken together, 1-pyrrolidinyl, lower alkyl-1-pyrrolidinyl, piperidino, lower alkylpiperidino, 4 - phenylpiperidino, 4 - halophenylpiperidino, morpholino, lower alkylmorpholino, hexamethyleneimino, 1-piperazinyl, 4-lower alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-phenyl-1-piperazinyl, 4-(lower alkoxyphenyl)-1-piperazinyl, 4-trifluoromethylphenyl - 1 - piperazinyl, 4-(loweralkylphenyl)-1-piperazinyl, 4 - halophenyl-1-piperazinyl, 3,6-dihydro-4-phenyl-1(2H)-pyridyl, 4-loweralkylphenyl - 3,6 - dihydro-1(2H)pyridyl, 3,6-dihydro-4-halophenyl - 1(2H)pyridyl, and azabicyclo[3.2.2]nonan-3-yl; and acid addition salts thereof.

2. A benzodiazepin-2-one according to claim 1: 3-(2-diloweralkylaminoethyl) - 1,3,4,5 - tetrahydro - 2H - 1,3-benzodiazepin-2-one.

3. The benzodiazepin-2-one according to claim 1: 3-(2-dimethylaminoethyl) - 1,3,4,5 - tetrahydro - 2H - 1,3-benzodiazepin-2-one.

4. The benzodiazepin-2-one according to claim 1: 3-(2-pyrrolidinoethyl) - 1,3,4,5 - tetrahydro - 2H - 1,3 - benzodiazepin-2-one.

5. The benzodiazepin-2-one according to claim 1: 3-(2-dimethylaminoethyl) - 8 - isopropyl - 1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one.

6. The benzodiazepin-2-one according to claim 1: 8-chloro - 3 - (2 - dimethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one.

7. The benzodiazepin-2-one according to claim 1: 6-chloro - 3 - (2 - dimethylaminoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one.

8. The benzodiazepin-2-one according to claim 1: 8-chloro 3 - (2 - pyrrolidinoethyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one.

9. The benzodiazepin-2-one according to claim 1: 3-(2-dimethylaminoethyl) - 8 - methyl-1,3,4,5-tetrahydro-2H-2H-1,3-benzodiazepin-2-one.

10. The benzodiazepin-2-one according to claim 1: 3-(2 - benzylmethylaminoethyl) - 1,3,4,5-tetrahydro - 2H-1,3-benzodiazepin-2-one.

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