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3,734,922

CERTAIN 4H-s-TRIAZOLO[4,3-a][1,4] BENZODIAZEPINES

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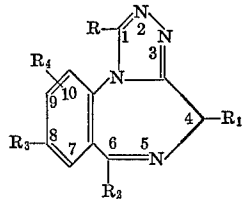
U.S. Cl. 260—296 T 2 Claims

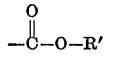
ABSTRACT OF THE DISCLOSURE

This invention relates to novel 4H-s-triazolo[4,3-a]-[1,4]benzodiazepines embraced by the formula



I

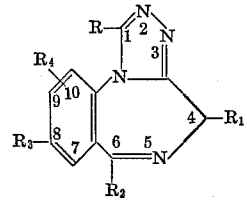
wherein R is selected from the group consisting of hydrogen, lower alkyl of 1 through 3 carbon atoms, phenyl, benzyl, nitromethyl, cyanomethyl, lower alkoxymethyl having an alkoxyl moiety of 1 through 3 carbon atoms, lower dialkylaminomethyl having an alkyl moiety of 1 through 3 carbon atoms, lower alkylthiomethyl having an alkyl moiety of 1 through 3 carbon atoms, pyrrolidinomethyl,



wherein R' is lower alkyl of 1 through 3 carbon atoms; R_1 is selected from the group consisting of hydrogen and lower alkyl of 1 through 3 carbon atoms; R_2 is selected from the group consisting of pyridyl, 2-pyrimidyl, furyl, pyrryl, thienyl, lower alkyl of 1 through 3 carbon atoms, lower alkenyl of 2 through 3 carbon atoms, cycloalkyl of 5 through 7 carbon atoms and cycloalkenyl of 5 through 7 carbon atoms; R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl of 1 through 3 carbon atoms, halogen, nitro, trifluoromethyl and lower alkoxy, lower alkylthio and lower dialkylamino wherein their lower alkyl moieties are of from 1 through 3 carbon atoms; and pharmacologically acceptable acid addition salts thereof. The new products of Formula I are useful as sedatives, hynotics, tranquilizers, muscle relaxants and anticonvulsants in mammals and birds. Also, as feed additives for increasing growth rate and feed efficiency of livestock.

BRIEF SUMMARY OF THE INVENTION

The novel 4H-s-triazolo[4,3-a][1,4]benzodiazepines of the formula



I

wherein R is selected from the group consisting of hydrogen, lower alkyl of 1 through 3 carbon atoms, phenyl, benzyl, nitromethyl, cyanomethyl, lower alkoxymethyl having an alkoxyl moiety of 1 through 3 carbon atoms, lower dialkylaminomethyl having an alkyl moiety of 1 through 3 carbon atoms, lower alkylthiomethyl having an

alkyl moiety of 1 through 3 carbon atoms, pyrrolidinomethyl,

wherein R' is lower alkyl of 1 through 3 carbon atoms; R_1 is selected from the group consisting of hydrogen and lower alkyl of 1 through 3 carbon atoms; R_2 is selected from the group consisting of pyridyl, 2-pyrimidyl, furyl, pyrryl, thienyl, lower alkyl of 1 through 3 carbon atoms, lower alkenyl of 2 through 3 carbon atoms, cycloalkyl of 5 through 7 carbon atoms and cycloalkenyl of 5 through 7 carbon atoms; R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl of 1 through 3 carbon atoms, halogen, nitro, trifluoromethyl, lower alkoxy, lower alkylthio and lower dialkylamino wherein the lower alkyl moiety is of from 1 through 3 carbon atoms; and pharmacologically acceptable acid addition salts thereof.

Examples of lower alkyl include methyl, ethyl, propyl and isopropyl. Examples of lower alkoxymethyl include methoxymethyl, ethoxymethyl, propoxymethyl and isopropoxymethyl. Examples of lower (dialkylamino)methyl include

(dimethylamino)methyl,
(diethylamino)methyl,
(methylethylamino)methyl,
(methylpropylamino)methyl,
(ethylpropylamino)methyl,
(dipropylamino)methyl and
(diisopropylamino)methyl.

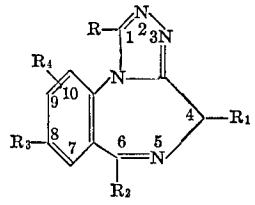
Examples of lower alkylthiomethyl include

(methylthio)methyl,
(ethylthio)methyl,
(propylthio)methyl and
(isopropylthio)methyl.

Examples of lower alkenyl of 2 through 3 carbon atoms include vinyl, 1-propenyl, allyl and isopropenyl. Examples of cycloalkyl of 5 through 7 carbon atoms include cyclopentyl, cyclohexyl and cycloheptyl. Examples of cycloalkenyl of 5 through 7 carbon atoms include 1-cyclopentyl, 1-cyclohexenyl and 1-cycloheptenyl. Examples of halogen include fluoro, chloro, bromo and iodo. Examples of lower alkoxy include methoxy, ethoxy, propoxy and isopropoxy. Examples of lower alkylthio include methylthio, ethylthio, propylthio and isopropylthio. Examples of lower dialkylamino include dimethylamino, diethylamino, dipropylamino, diisopropylamino, methylethylamino, methylpropylamino, ethylpropylamino, methylisopropylamino and ethylisopropylamino.

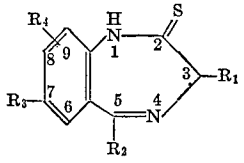
The novel 4H-s-triazolo[4,3-a][1,4]benzodiazepines of Formula I exist either in the non-protonated (free base) from or in the protonated (acid addition salt) form, depending on the pH of the environment. They form stable protonates, i.e., pharmacologically acceptable acid addition salts, on acidification of the free base with suitable pharmacologically acceptable acids, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, acetic, propionic palmitic, benzoic, salicylic, hexynoic, phenylbutyric, naphthoic, glycolic, succinic, nicotinic, tartaric, maleic, malic, pamoic, methanesulfonic, cyclohexanesulfonic, picric and lactic acids, and the like. Conversely, the free bases of the novel compounds of Formula I can be obtained from a salt (e.g., from the hydrochloride or sulfate salt), by neutralization with a base such as sodium hydroxide, extracting with an immiscible solvent, for example chloroform, drying the extract, for example with anhydrous sodium sulfate, and removing the solvent by evaporation.

A compound of the formula



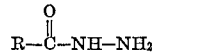
(I)

wherein R, R_1, R_2, R_3 and R_4 have the same meaning as above, is prepared by condensing a corresponding compound of the formula



(II)

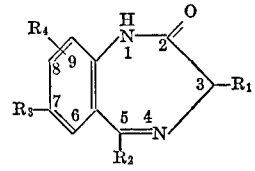
wherein R_1, R_2, R_3 and R_4 have the same meaning as above, with a corresponding hydrazide of the formula



III

wherein R has the same meaning as above.

An appropriate starting material of Formula II can be prepared by heating a known corresponding compound of the formula



IV

wherein R_1, R_2, R_3 and R_4 have the same meaning as above, with phosphorus pentasulfide in a solvent such as pyridine, benzene, toluene or xylene at between about 80 to about 140° C. for between about 30 minutes to about 6 hours. The preparation of compounds of Formula IV are described in U.S. Pats. 3,100,770; 3,179,656; 3,268,586; 3,338,886; and 3,466,328; Belgian Pats. 619,101 and 662,240; French Pats. 1,391,752 and 1,455,048; Netherlands Pats. 65/07637, 67/08568 and 69/08966; and J. Pharm. Sci. 53, 264.

In carrying out the process for the production of a compound of Formula I of this invention, an appropriate thione starting material (II), in an inert organic solvent (preferably a lower alkanol, e.g., methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, or dioxane, dimethyl sulfoxide or the like) is heated to between about 60 to about 140° C. (preferably at reflux temperature) with a desired corresponding acid hydrazide of Formula III. Nitrogen is usually bubbled through the mixture to remove the hydrogen sulfide formed in the reaction. In a preferred embodiment, the acid hydrazide is used in excess, such as from about 2 to about 5 times the theoretically required amount, but the reaction is operative with smaller or larger amounts. The reaction period is between about 1 to about 48 hours. At the termination of the reaction, the product (I) can be isolated from the reaction mixture by conventional means, for example, when a water-miscible solvent is used, by pouring the reaction mixture into the water and separating the resulting precipitate by filtration or by extraction with water-immiscible solvents. Additional purification of the product can be accomplished by conventional means, for example, by elution chromatography from an adsorbent column with a suitable solvent such as acetone, ethyl acetate, ether, methylene chloride or Skellysolve B (hexanes), mixtures and combinations of these solvents; also by gradient elution chromatography from an adsorbent column with a suitable mixture of solvents, such as methylene chloride-Skellysolve B, acetone-Skellysolve B, and the like.

The novel compounds of Formula I and the pharmacologically acceptable acid addition salts thereof have sedative, hypnotic, anticonvulsant, tranquilizing and muscle relaxant effects in mammals and birds, and as feed additives for increasing the growth rate and feed efficiency of livestock poultry.

Sedative effects of the compound of this invention are shown by the following tests in mice:

Chimney test: [Med. Exp. 4, 145 (1961)]: The test determines the ability of mice to back up and out of a vertical glass cylinder within 30 seconds. At the effective dosage, 50% of the mice failed doing it.

Dish test: Mice in Petri dishes (10 cm. diameter, 5 cm. high, partially embedded in wood shavings), climb out in a very short time, when not treated. Mice remaining in the dish for more than 3 minutes indicates tranquilization. ED_{50} equals the dose of test compound at which 50% of the mice remain in the dish.

Pedestal test: The untreated mouse leaves a standard pedestal in less than a minute to climb back to the floor of the standard mouse box. Tranquilized mice will stay on the pedestal for more than 1 minute.

Nicotine antagonism test: Mice in a group of 6 are injected with the test compound. Thirty minutes later the mice including control (untreated) mice are injected with nicotine salicylate (2 mg./kg.). The control mice show overstimulation, i.e., (1) running convulsions followed by (2) tonic extensor fits; followed by (3) death.

Antagonism to strychnine (as sulfate): The test consists in orally administering into groups of 6 mice the test compound, and 30 minutes later 3 mg./kg. strychnine sulfate intraperitoneally. The survivors after 4 hours reflect the activity of the compound as a muscle relaxant and antispasmodic. A dosage of 3 mg./kg. of strychnine sulfate is routinely fatal to all the control mice.

The following compound typical of this invention has (by intraperitoneal injection) ED_{50} as shown in the table below.

Compound—8 - bromo - 1 - methyl - 6 - (2 - pyridyl)-4H-s - triazolo[4,3 - a][1,4]benzodiazepine (I):

	ED_{50} (in mg./kg.)
Ch	0.13
D	0.071
P	0.25
Ni	0.04
Str	0.5

Ch=chimney test
D=dish test
P=pedestal test
Ni=nicotine antagonism (3) test
Str=strychnine antagonism

The pharmaceutical forms contemplated by this invention include pharmaceutical compositions suited for oral, parenteral and rectal use, e.g., tablets, powder packets, cachets, dragees, capsules, solutions, suspensions, sterile injectable forms, suppositories, bougies, and the like. Suitable diluents or carriers such as carbohydrates (lactose), proteins, lipids, calcium phosphate, cornstarch, stearic acid, methylcellulose and the like can be used as carriers or for coating purposes. Oil, e.g., coconut oil, sesame oil, safflower oil, cottonseed oil, peanut oil can be used for preparing solutions or suspensions of the active drug. Sweetening, coloring, and flavoring agents can be added.

For mammals and birds food premixes, with starch, oatmeal, dried fishmeat, fishmeal, flour and the like can be prepared.

As tranquilizer the compounds of Formula I can be used in dosages of 0.01 mg. to 20.0 mg./kg. in oral or injectable preparations as described above, to alleviate tension and

anxiety in mammals, or birds, such as e.g. occurs when animals are travelling.

The following examples are illustrative of the processes and products of the present invention, but are not to be construed as limiting.

Example 1.—7 - bromo - 1,3 - dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione (II)

A stirred solution of 6.53 g. of 7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one (prepared as in J. Pharm. Sci. 53, 264) in 400 ml. of dry pyridine is heated in an oil bath, under nitrogen, with 5.05 g. of phosphorus pentasulfide at between about 110 to 120° C. for about 1 hour, cooled and concentrated under vacuum. Pyridine remaining in the residue is removed by the successive addition of xylene and toluene with vacuum concentration after each addition of solvent. The dark brown solid residue is triturated with a mixture of aqueous sodium carbonate solution and chloroform and the resulting finely divided tan solid is collected by filtration, washed with water, dissolved in a mixture of chloroform and ethanol, decolorized with activated carbon and crystallized to yield 3.39 g. of product melting at 249° C. (with decomposition); and 0.559 g. melting at 243° C. (with decomposition). The analytical sample is crystallized from ethanol to give pure 7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione, with a melting point of 245 to 246° C. (with decomposition) and ultaviolet spectrum (ethanol) which had end absorption, λ_{max} 219 mμ (ϵ=21,050), λ_{max} 302 mμ (ϵ=24,100).

Analysis.—Calcd. for $C_{14}H_{10}BrN_3S$ (percent): C. 50.61; H, 3.03; Br, 24.06; N, 12.65; S, 9.65. Found (percent): C, 49.82; H, 3.31; Br, 24.31; N, 12.60; S, 9.59.

Example 2.—7chloro-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione (II)

To a hot solution of 1 g. (5 mmoles) of 7-chloro-1,3-dihydro-5-methyl-2H-1,4-benzodiazepin-2-one (prepared as in French Patent 1,391,752) in 150 ml. of xylene, 1.1 g. (5 mmoles) of phosphorus pentasulfide is added. The mixture is heated under reflux in a nitrogen atmosphere for about 4 hours. The reaction mixture is cooled and filtered, with the filtrate containing only a small amount of material. The filtered solid is treated with hot water and filtered again. The filtrate is treated with 20% sodium hydroxide to give a pH of 6 to 8 and the white solid removed by extraction with ethyl acetate to give 129 mg. of crude product. The initial solid is again treated with water, the aqueous phase made basic with sodium bicarbonate and then extracted with hot ethyl acetate to give 1 g. of brown solid. This material plus the 129 mg. of crude product are chromatographed on 130 g. of silica gel using 50% ethyl acetate:50% cyclohexane as eluting solvent. The product taken from the column is recrystallized from ethyl acetate to give 455 mg. of product, having a melting point of 205 to 206° C. (with decomposition). A previously prepared sample of the product, 7-chloro-1,3-dihydro - 5 - methyl-2H-1,4-benzodiazepine-2-thione, melts at 201 to 203° C. and gives the analysis that follows.

Analysis.—Calcd. for $C_{10}H_9ClN_2S$ (percent): C, 53.45; H, 4.04; N, 12.47; Cl, 15.78; S, 14.27. Found (percent): C, 53.29; H, 3.87; N, 12.16; Cl, 15.88; S, 14.67.

Following the procedure of Examples 1 and 2 but substituting other known representative 2H-1,4-benzodiazepin-2-ones such as

(1) 7-bromo-1,3-dihydro-5-ethyl-2H-1,4-benzodiazepin-2-one,
(2) 1,3-dihydro-7-nitro-5-propyl-2H-1,4-benzodiazepin-2-one,
(3) 1,3-dihydro-3-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(4) 1,3-dihydro-7-fluoro-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(5) 7-chloro-1,3-dihydro-3-propyl-5-(3-pyridyl)-2H-1,4-benzodiazepin-2-one,
(6) 1,3-dihydro-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(7) 3-ethyl-1,3-dihydro-5-(4-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(8) 1,3-dihydro-3-propyl-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(9) 1,3-dihydro-7-methylthio-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(10) 1,3-dihydro-5-(3-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(11) 7-bromo-1,3-dihydro-5-(2-pyridyl)-8-nitro-2H-1,4-benzodiazepin-2-one,
(12) 7-chloro-1,3-dihydro-5-(3-pyridyl)-9-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(13) 7-fluoro-1,3-dihydro-3-propyl-5-(4-pyridyl)-8-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(14) 1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(15) 1,3-dihydro-7-iodo-9-nitro-5-(3-pyridyl)-2H-1,4-benzodiazepin-2-one,
(16) 7-chloro-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(17) 1,3-dihydro-7-nitro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(18) 7-bromo-1,3-dihydro-9-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(19) 7-bromo-1,3-dihydro-3-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(20) 7-chloro-1,3-dihydro-3-ethyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(21) 7-bromo-1,3-dihydro-3-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(22) 1,3-dihydro-7-fluoro-3-propyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(23) 7-chloro-1,3-dihydro-5-(2-pyrryl)-2H-1,4-benzodiazepin-2-one,
(24) 1,3-dihydro-5-(2-pyrryl)-2H-1,4-benzodiazepin-2-one,
(25) 1,3-dihydro-7-nitro-5-(2-thienyl)-2H-1,4-benzodiazepin-2-one,
(26) 1,3-dihydro-9-methoxy-5-(2-thienyl)-2H-1,4-benzodiazepin-2-one,
(27) 7-chloro-1,3-dihydro-5-(2-thienyl)-2H-1,4-benzodiazepin-2-one,
(28) 7-bromo-1,3-dihydro-8-ethyl-5-(2-thienyl)-2H-1,4-benzodiazepin-2-one,
(29) 7-chloro-1,3-dihydro-9-propyl-5-(2-thienyl)-2H-1,4-benzodiazepin-2-one,
(30) 7-diethylamino-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(31) 1,3-dihydro-9-methylthio-7-nitro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(32) 7-bromo-8-fluoro-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(33) 7-chloro-1,3-dihydro-8-ethoxy-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(34) 1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(35) 7-bromo-1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(36) 1,3-dihydro-7-nitro-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(37) 7-chloro-1,3-dihydro-9-ethyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(38) 1,3-dihydro-7-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(39) 7-bromo-1,3-dihydro-8-ethyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(40) 7-chloro-1,3-dihydro-9-propyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(41) 7-bromo-1,3-dihydro-5-(2-furyl)-2H-1,4-benzodiazepin-2-one,
(42) 1,3-dihydro-5-(4-furyl)-2H-1,4-benzodiazepin-2-one,

(43) 1,3-dihydro-3-methyl-7-nitro-5-(4-furyl)-2H-1,4-benzodiazepin-2-one,
(44) 7-bromo-1,3-dihydro-9-ethoxy-5-(2-pyrryl)-2H-1,4-benzodiazepin-2-one,
(45) 8-chloro-1,3-dihydro-5-(2-thienyl)-2H-1,4-benzodiazepin-2-one,
(46) 7-bromo-1,3-dihydro-3-ethyl-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(47) 1,3-dihydro-7-nitro-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(48) 9-chloro-1,3-dihydro-3-methyl-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(49) 7-bromo-1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(50) 1,3-dihydro-7-methylthio-5-(2-pyrimidyl)-9-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(51) 7-chloro-8-diethylamino-1,3-dihydro-9-propoxy-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(52) 7-dipropylamino-9-chloro-3-ethyl-1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(53) 7,8-dibromo-1,3-dihydro-3-methyl-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(54) 7-chloro-1,3-dihydro-5-(1-cyclopentenyl)-2H-1,4-benzodiazepin-2-one,
(55) 7-bromo-1,3-dihydro-5-(1-cyclohexenyl)-2H-1,4-benzodiazepin-2-one,
(56) 1,3-dihydro-5-(1-cycloheptenyl)-7-nitro-2H-1,4-benzodiazepin-2-one,
(57) 7-chloro-1,3-dihydro-5-cyclopentyl-2H-1,4-benzodiazepin-2-one,
(58) 1,3-dihydro-5-cyclopentyl-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(59) 3-ethyl-1,3-dihydro-5-cyclohexyl-7-propoxy-2H-1,4-benzodiazepin-2-one,
(60) 7-chloro-9-diethylamino-1,3-dihydro-5-cyclopentyl-2H-1,4-benzodiazepin-2-one,
(61) 7-bromo-1,3-dihydro-5-vinyl-2H-1,4-benzodiazepin-2-one,
(62) 1,3-dihydro-3,5-dimethyl-7-nitro-2H-1,4-benzodiazepin-2-one,
(63) 7-ethylthio-1,3-dihydro-5-propyl-2H-1,4-benzodiazepin-2-one,
(64) 1,3-dihydro-5-(1-propenyl)-7-fluoro-2H-1,4-benzodiazepin-2-one,
(65) 1,3-dihydro-5-isopropenyl-7-propoxy-2H-1,4-benzodiazepin-2-one,
(66) 7-chloro-1,3-dihydro-3-ethyl-5-cyclohexyl-2H-1,4-benzodiazepin-2-one,
(67) 7-bromo-1,3-dihydro-5-cyclohexyl-2H-1,4-benzodiazepin-2-one,
(68) 7-chloro-1,3-dihydro-3,8-dimethyl-5-cyclohexyl-2H-1,4-benzodiazepin-2-one,
(69) 7-chloro-1,3-dihydro-3-ethyl-5-methyl-2H-1,4-benzodiazepin-2-one,
(70) 7-bromo-1,3-dihydro-5-ethyl-8-nitro-2H-1,4-benzodiazepin-2-one,
(71) 7-chloro-1,3-dihydro-5-vinyl-2H-1,4-benzodiazepin-2-one,
(72) 7-bromo-1,3-dihydro-5-methyl-2H-1,4-benzodiazepin-2-one,
(73) 1,3-dihydro-5-(1-propenyl)-8-nitro-3-propyl-2H-1,4-benzodiazepin-2-one,
(74) 1,3-dihydro-3,5-diethyl-9-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(75) 1,3-dihydro-8-ethylthio-5-ethyl-7-fluoro-2H-1,4-benzodiazepin-2-one,
(76) 1,3-dihydro-5-propyl-8-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(77) 8-bromo-1,3-dihydro-5-(2-pyridyl)-7-nitro-2H-1,4-benzodiazepin-2-one,
(78) 7-bromo-1,3-dihydro-5-ethyl-9-propylthio-2H-1,4-benzodiazepin-2-one,
(79) 7-chloro-1,3-dihydro-5-cycloheptyl-2H-1,4-benzodiazepin-2-one,

(80) 8-chloro-1,3-dihydro-5-(1-cyclopentenyl)-2H-1,4-benzodiazepin-2-one,
(81) 9-chloro-7-fluoro-1,3-dihydro-5-methyl-2H-1,4-benzodiazepin-2-one,
(82) 1,3-dihydro-5-ethyl-9-fluoro-2H-1,4-benzodiazepin-2-one,
(83) 1,3-dihydro-5-isopropenyl-2H-1,4-benzodiazepin-2-one,
(84) 1,3-dihydro-5-methyl-2H-1,4-benzodiazepin-2-one,
(85) 1,3-dihydro-5-propyl-2H-1,4-benzodiazepin-2-one,
(86) 7-chloro-9-ethoxy-1,3-dihydro-5-methyl-2H-1,4-benzodiazepin-2-one,
(87) 1,3-dihydro-7-dimethylamino-5-methyl-2H-1,4-benzodiazepin-2-one,
(88) 1,3-dihydro-5-ethyl-7-iodo-2H-1,4-benzodiazepin-2-one,
(89) 8-bromo-1,3-dihydro-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(90) 7-ethoxy-1,3-dihydro-5-ethyl-2H-1,4-benzodiazepin-2-one,
(91) 1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepin-2-one,
(92) 8-fluoro-1,3-dihydro-7-nitro-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(93) 1,3-dihydro-5-methyl-8-nitro-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(94) 7-bromo-1,3-dihydro-9-propoxy-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one,
(95) 7-chloro-6-fluoro-1,3-dihydro-5-propyl-2H-1,4-benzodiazepin-2-one,
(96) 1,3-dihydro-5-(2-pyrryl)-8-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(97) 7-chloro-1,3-dihydro-5-(2-thienyl)-9-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(98) 7,9-dichloro-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one,
(99) 1,3-dihydro-5-(2-pyrimidyl)-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one,
(100) 7-chloro-1,3-dihydro-8-methylthio-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one, etc.,

yields, respectively,

(1) 7-bromo-1,3-dihydro-5-ethyl-2H-1,4-benzodiazepine-2-thione,
(2) 1,3-dihydro-7-nitro-5-propyl-2H-1,4-benzodiazepine-2-thione,
(3) 1,3-dihydro-3-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(4) 1,3-dihydro-7-fluoro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(5) 7-chloro-1,3-dihydro-3-propyl-5-(3-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(6) 1,3-dihydro-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(7) 3-ethyl-1,3-dihydro-5-(4-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(8) 1,3-dihydro-3-propyl-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(9) 1,3-dihydro-7-methylthio-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(10) 1,3-dihydro-5-(3-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(11) 7-bromo-1,3-dihydro-5-(2-pyridyl)-8-nitro-2H-1,4-benzodiazepine-2-thione,
(12) 7-chloro-1,3-dihydro-5-(3-pyridyl)-9-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(13) 7-fluoro-1,3-dihydro-3-propyl-5-(4-pyridyl)-8-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(14) 1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(15) 1,3-dihydro-7-iodo-9-nitro-5-(3-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(16) 7-chloro-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,

(17) 1,3-dihydro-7-nitro-5-2-(pyridyl)-2H-1,4-benzodiazepine-2-thione,
(18) 7-bromo-1,3-dihydro-9-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(19) 7-bromo-1,3-dihydro-3-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(20) 7-chloro-1,3-dihydro-3-ethyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(21) 7-bromo-1,3-dihydro-3-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(22) 1,3-dihydro-7-fluoro-3-propyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(23) 7-chloro-1,3-dihydro-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione,
(24) 1,3-dihydro-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione,
(25) 1,3-dihydro-7-nitro-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione,
(26) 1,3-dihydro-9-methoxy-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione,
(27) 7-chloro-1,3-dihydro-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione,
(28) 7-bromo-1,3-dihydro-8-ethyl-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione,
(29) 7-chloro-1,3-dihydro-9-propyl-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione,
(30) 7-diethylamino-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(31) 1,3-dihydro-9-methylthio-7-nitro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(32) 7-bromo-8-fluoro-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(33) 7-chloro-1,3-dihydro-8-ethoxy-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(34) 1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(35) 7-bromo-1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(36) 1,3-dihydro-7-nitro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(37) 7-chloro-1,3-dihydro-9-ethyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(38) 1,3-dihydro-7-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(39) 7-bromo-1,3-dihydro-8-ethyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(40) 7-chloro-1,3-dihydro-9-propyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(41) 7-bromo-1,3-dihydro-5-(2-furyl)-2H-1,4-benzodiazepine-2-thione,
(42) 1,3-dihydro-5-(4-furyl)-2H-1,4-benzodiazepine-2-thione,
(43) 1,3-dihydro-3-methyl-7-nitro-5-(4-furyl)-2H-1,4-benzodiazepine-2-thione,
(44) 7-bromo-1,3-dihydro-9-ethoxy-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione,
(45) 8-chloro-1,3-dihydro-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione,
(46) 7-bromo-1,3-dihydro-3-ethyl-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(47) 1,3-dihydro-7-nitro-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(48) 9-chloro-1,3-dihydro-3-methyl-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(49) 7-bromo-1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(50) 1,3-dihydro-7-methylthio-5-(2-pyrimidyl)-9-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(51) 7-chloro-8-diethylamino-1,3-dihydro-9-propoxy-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(52) 7-dipropylamino-9-chloro-3-ethyl-1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(53) 7,8-dibromo-1,3-dihydro-3-methyl-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(54) 7-chloro-1,3-dihydro-5-(1-cyclopentenyl)-2H-1,4-benzodiazepine-2-thione,
(55) 7-bromo-1,3-dihydro-5-(1-cyclohexenyl)-2H-1,4-benzodiazepine-2-thione,
(56) 1,3-dihydro-5-(1-cycloheptenyl)-7-nitro-2H-1,4-benzodiazepine-2-thione,
(57) 7-chloro-1,3-dihydro-5-cyclopentyl-2H-1,4-benzodiazepine-2-thione,
(58) 1,3-dihydro-5-cyclopentyl-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(59) 3-ethyl-1,3-dihydro-5-cyclohexyl-7-propoxy-2H-1,4-benzodiazepine-2-thione,
(60) 7-chloro-9-diethylamino-1,3-dihydro-5-cyclopentyl-2H-1,4-benzodiazepine-2-thione,
(61) 7-bromo-1,3-dihydro-5-vinyl-2H-1,4-benzodiazepine-2-thione,
(62) 1,3-dihydro-3,5-dimethyl-7-nitro-2H-1,4-benzodiazepine-2-thione,
(63) 7-ethylthio-1,3-dihydro-5-propyl-2H-1,4-benzodiazepine-2-thione,
(64) 1,3-dihydro-5-1(-propenyl)-7-fluoro-2H-1,4-benzodiazepine-2-thione,
(65) 1,3-dihydro-5-isopropenyl-7-propoxy-2H-1,4-benzodiazepine-2-thione,
(66) 7-chloro-1,3-dihydro-3-ethyl-5-cyclohexyl-2H-1,4-benzodiazepine-2-thione,
(67) 7-bromo-1,3-dihydro-5-cyclohexyl-2H-1,4-benzodiazepine-2-thione,
(68) 7-chloro-1,3-dihydro-3,8-dimethyl-5-cyclohexyl-2H-1,4-benzodiazepine-2-thione,
(69) 7-chloro-1,3-dihydro-3-ethyl-5-methyl-2H-1,4-benzodiazepine-2-thione,
(70) 7-bromo-1,3-dihydro-5-ethyl-8-nitro-2H-1,4-benzodiazepine-2-thione,
(71) 7-chloro-1,3-dihydro-5-vinyl-2H-1,4-benzodiazepine-2-thione,
(72) 7-bromo-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione,
(73) 1,3-dihydro-5-(1-propenyl)-8-nitro-3-propyl-2H-1,4-benzodiazepine-2-thione,
(74) 1,3-dihydro-3,5-diethyl-9-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(75) 1,3-dihydro-8-ethylthio-5-ethyl-7-fluoro-2H-1,4-benzodiazepine-2-thione,
(76) 1,3-dihydro-5-propyl-8-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(77) 8-bromo-1,3-dihydro-5-(2-pyridyl)-7-nitro-2H-1,4-benzodiazepine-2-thione,
(78) 7-bromo-1,3-dihydro-5-ethyl-9-propylthio-2H-1,4-benzodiazepine-2-thione,
(79) 7-chloro-1,3-dihydro-5-cycloheptyl-2H-1,4-benzodiazepine-2-thione,
(80) 8-chloro-1,3-dihydro-5-(1-cyclopentenyl)-2H-1,4-benzodiazepine-2-thione,
(81) 9-chloro-7-fluoro-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione,
(82) 1,3-dihydro-5-ethyl-9-fluoro-2H-1,4-benzodiazepine-2-thione,
(83) 1,3-dihydro-5-isopropenyl-2H-1,4-benzodiazepine-2-thione,
(84) 1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione,
(85) 1,3-dihydro-5-propyl-2H-1,4-benzodiazepine-2-thione,
(86) 7-chloro-9-ethoxy-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione,
(87) 1,3-dihydro-7-dimethylamino-5-methyl-2H-1,4-benzodiazepine-2-thione,
(88) 1,3-dihydro-5-ethyl-7-iodo-2H-1,4-benzodiazepine-2-thione,
(89) 8-bromo-1,3-dihydro-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(90) 7-ethoxy-1,3-dihydro-5-ethyl-2H-1,4-benzodiazepine-2-thione,

(91) 1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione,
(92) 1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(93)- 1,3-dihydro-5-methyl-8-nitro-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(94) 7-bromo-1,3-dihydro-9-propoxy-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(95) 7-chloro-6-fluoro-1,3-dihydro-5-propyl-2H-1,4-benzodiazepine-2-thione,
(96) 1,3-dihydro-5-(2-pyrryl)-8-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(97) 7-chloro-1,3-dihydro-5-(2-thienyl)-9-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(98) 7,9-dichloro-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione,
(99) 1,3-dihydro-5-(2-pyrimidyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione,
(100) 7-chloro-1,3-dihydro-8-methylthio-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione, etc.

Example 3.—8-bromo-1-methyl-6-(2-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I)

A mixture of 4.48 g. (0.0135 mole) of 7-bromo-1,3-dihydro - 5 - (2-pyridyl)-2H-1,4-benzodiazepine-2-thione (obtained as in Example 1), 3.06 g. (0.041 mole) of acethydrazide and 200 ml. of n-butyl alcohol is refluxed for about 12 hours with a slow stream of nitrogen bubbling through it. The mixture is concentrated under vacuum and the residue suspended in water and extracted with chloroform. The extract is washed with water, dried with potassium carbonate and concentrated under vacuum. The resulting residue is crystallized twice from a mixture of methanol and ethyl acetate to give 1.97 g. of 8 - bromo - 1 - methyl - 6 - (2 - pyridyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine (I), having a melting point of 253 to 254° C. The analytical sample is crystallized from the same solvents to give a melting point of 253.5 to 255° C., uv (ethanol) $\lambda_{max.}$ 223 mμ (ϵ=32,900), 270 (inflection, 6650), 297 (inflection, 1850).

Analysis.—Calcd. for $C_{16}H_{12}BrN_5$ (percent): C, 54.25; H, 3.42; Br, 22.56; N, 19.77. Found (percent): C, 54.02; H, 3.24; Br, 22.62; N, 17.53.

Example 4.—8-chloro-1,6-dimethyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepine (I)

A solution of 581 mg. (2.6 mmoles) of 7-chloro-1,3-dihydro - 5 - methyl - 2H - 1,4 - benzodiazepine-2-thione (obtained as in Example 2) and 576 mg. (7.8 mmoles) of acethydrazide in 50 ml. of n-butanol is heated under reflux for about 6 hours. During the first few hours, a stream of nitrogen is passed through the reaction mixture; for the remaining time the reaction is maintained under an atmosphere of nitrogen. The reaction mixture is successively concentrated, treated with chloroform, washed with water and then brine. Concentration of the organic layer gives a residue that is chromatographed on a column of silica gel using 10% methanol:90% chloroform as eluting solvent. The product is removed as an oil which solidifies upon treatment with ethyl acetate. It is recrystallized from ethyl acetate to yield 8-chloro-1,6-dimethyl - 4H - s - triazolo[4,3-a][1,4]benzodiazepine (I), melting at 219 to 219.5° C.

Analysis.—Calcd. for $C_{12}H_{11}ClN_4$ (percent): C, 58.42; H, 4.50; Cl, 14.37; N, 22.72. Found (percent): C, 58.33; H, 4.22; Cl, 14.11; N, 22.33.

Following the procedure of Examples 3 and 4 but substituting another known representative 2H-1,4-benzodiazepine-2-thione starting material (obtained as in Examples 1 and 2 and the paragraph following Example 2) and reacting it with acethydrazide or another representative known hydrazide, such as

(1) 7-chloro-1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione and acethydrazide,
(2) 7-bromo-1,3-dihydro-3,5-dimethyl-2H-1,4-benzodiazepine-2-thione and acethydrazide,
(3) 1,3-dihydro-3-ethyl-7-fluoro-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione and acethydrazide,
(4) 7,9-dichloro-1,3-dihydro-3-propyl-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione and acethydrazide,
(5) 7-bromo-1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione and acethydrazide,
(6) 1,3-dihydro-3-methyl-7-nitro-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione and formic acid hydrazide,
(7) 1,3-dihydro-5-cyclopentyl-3-methyl-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and formic acid hydrazide,
(8) 7-chloro-1,3-dihydro-5-cycloheptyl-3-ethyl-2H-1,4-benzodiazepine-2-thione and formic acid hydrazide,
(9) 7-dimethylamino-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione and butyric acid hydrazide,
(10) 1,3-dihydro-3-methyl-5-(2-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and isobutyric acid hydrazide,
(11) 7-bromo-1,3-dihydro-5-propyl-2H-1,4-benzodiazepine-2-thione and benzoic acid hydrazide,
(12) 1,3-dihydro-7-nitro-5-vinyl-2H-1,4-benzodiazepine-2-thione and benzoic acid hydrazide,
(13) 9-chloro-1,3-dihydro-5-(4-pyridyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and phenylacetic acid hydrazide,
(14) 1,3-dihydro-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione and nitroacetic acid hydrazide,
(15) 1,3-dihydro-7-iodo-8-nitro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione and cyanoacetic acid hydrazide,
(16) 3-ethyl-1,3-dihydro-7-nitro-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione and methoxyacetic acid hydrazide,
(17) 7-chloro-1,3-dihydro-5-(1-propenyl)-2H-1,4-benzodiazepine-2-thione and dimethylaminoacetic acid hydrazide,
(18) 1,3-dihydro-5-(2-furyl)-7-methylthio-9-nitro-2H-1,4-benzodiazepine-2-thione and (methylpropylamino)acetic acid hydrazide,
(19) 7,8-dibromo-1,3-dihydro-3-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione and (diethylamino) acetic acid hydrazide,
(20) 7-chloro-1,3-dihydro-5-(1-cyclopentenyl)-2H-1,4-benzodiazepine-2-thione and (methylethylamino)acetic acid hydrazide,
(21) 1,3-dihydro-5-ethyl-7-fluoro-2H-1,4-benzodiazepine-2-thione and (diethylamino)acetic acid hydrazide,
(22) 7-bromo-1,3-dihydro-5-propyl-2H-1,4-benzodiazepine-2-thione and (ethylpropylamino)acetic acid hydrazide,
(23) 1,3-dihydro-5-(1-cyclohexenyl)-7-nitro-3-propyl-2H-1,4-benzodiazepine-2-thione and pyrrolidinoacetic acid hydrazide,
(24) 8-chloro-1,3-dihydro-5-(2-furyl)-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and pyrrolidinoacetic acid hydrazide,
(25) 9-chloro-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione and (dipropylamino)acetic acid hydrazide,
(26) 1,3-dihydro-5-ethyl-9-fluoro-2H-1,4-benzodiazepine-2-thione and (diisopropylamino)acetic acid hydrazide,
(27) 7-bromo-1,3-dihydro-5-propyl-2H-1,4-benzodiazepine-2-thione and propoxyacetic acid hydrazide,
(28) 8-bromo-1,3-dihydro-5-(1-cycloheptenyl)-3-

ethyl-2H-1,4-benzodiazepine-2-thione and methoxyacetic acid hydrazide,
(29) 7-chloro-1,3-dihydro-5-cyclohexyl-2H-1,4-benzodiazepine-2-thione and formic acid hydrazide,
(30) 8-bromo-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione and butyric acid hydrazide,
(31) 7,8-dibromo-1,3-dihydro-5-ethyl-2H-1,4-benzodiazepine-2-thione and (methylthio) acetic acid hydrazide,
(32) 1,3-dihydro-3,5-diethyl-8-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and (ethylthio)acetic acid hydrazide,
(33) 9-chloro-1,3-dihydro-5-cyclopentyl-3-ethyl-2H-1,4-benzodiazepine-2-thione and (propylthio) acetic acid hydrazide,
(34) 1,3-dihydro-7-nitro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-thione and (isopropylthio)acetic acid hydrazide,
(35) 8-bromo-1,3-dihydro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione and methoxyacetic acid hydrazide,
(36) 1,3-dihydro-5-(2-pyrimidyl)-2H-1,4-benzodiazepine-2-thione and formic acid hydrazide,
(37) 7-chloro-1,3-dihydro-5-methyl-2H-1,4-benzodiazepine-2-thione and benzoic acid hydrazide,
(38) 1,3-dihydro-9-fluoro-5-(2-pyrryl)-2H-1,4-benzodiazepine-2-thione and benzoic acid hydrazide,
(39) 1,3-dihydro-3-ethyl-7-fluoro-5-(2-furyl)-2H-1,4-benzodiazepine-2-thione and phenylacetic acid hydrazide,
(40) 7-bromo-8-chloro-1,3-dihydro-5-cyclopentyl-2H-1,4-benzodiazepine-2-thione and phenylacetic acid hydrazide,
(41) 8-bromo-1,3-dihydro-5-cyclopentyl-7-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and methoxyacetic acid hydrazide,
(42) 7-bromo-1,3-dihydro-5-cyclohexyl-7-nitro-2H-1,4-benzodiazepine-2-thione and cyanoacetic acid hydrazide,
(43) 8-bromo-1,3-dihydro-5-cycloheptyl-3-propyl-2H-1,4-benzodiazepine-2-thione and nitroacetic acid hydrazide,
(44) 7-chloro-1,3-dihydro-5-isopropenyl-3-methyl-2H-1,4-benzodiazepine-2-thione and nitroacetic acid hydrazide,
(45) 8-chloro-1,3-dihydro-3-ethyl-7-nitro-5-(4-pyridyl)-2H-1,4-benzodiazepine-2-thione and oxalic acid hydrazide, methyl ester,
(46) 7-bromo-1,3-dihydro-5-(2-furyl)-2H-1,4-benzodiazepine-2-thione and oxalic acid hydrazide, methyl ester,
(47) 7-bromo-1,3-dihydro-5-(1-cyclohexenyl)-9-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and oxalic acid ethyl ester, hydrazide,
(48) 1,3-dihydro-3,5-dimethyl-7-propoxy-2H-1,4-benzodiazepine-2-thione and oxalic acid hydrazide, propyl ester,
(49) 1,3-dihydro-3-ethyl-5-propyl-8-trifluoromethyl-2H-1,4-benzodiazepine-2-thione and oxalic acid hydrazide, propyl ester,
(50) 7,9-dichloro-1,3-dihydro-3-ethyl-5-(2-thienyl)-2H-1,4-benzodiazepine-2-thione and oxalic acid hydrazide, isopropyl ester, etc.

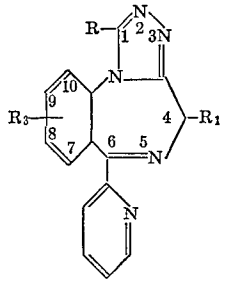
yields, respectively.

(1) 8-chloro-1-methyl-6-(4-pyridyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine (I),
(2) 8-bromo-1,4,6-trimethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(3) 4-ethyl-8-fluoro-1-methyl-6-(2-pyrryl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(4) 8,10-dichloro-1-methyl-4-propyl-6-(2-thienyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(5) 8-bromo-1-methyl-6-(4-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(6) 4-methyl-8-nitro-6-(2-pyrimidyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(7) 6-cyclopentyl-4-methyl-8-trifluoromethyl-4H-s-triazolo[4,3-a[1,4]benzodiazepine (I)
(8) 8-chloro-6-cycloheptyl-4-ethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(9) 8-dimethylamino-6-methyl-1-propyl-4H-triazolo-[4,3-a][1,4]benzodiazepine (I),
(10) 1-isopropyl-4-methyl-6-(2-pyridyl)-8-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(11) 8-bromo-1-phenyl-6-propyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(12) 8-nitro-6-vinyl-1-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(13) 1-benzyl-10-chloro-6-(4-pyridyl)-8-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(14) 1-nitromethyl-6-(2-pyrryl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(15) 1-cyanomethyl-8-iodo-9-nitro-6-(2-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(16) 4-ethyl-1-methoxymethyl-8-nitro-6-(2-pyrryl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(17) 8-chloro-1-(dimethylamino)methyl-6-(1-propenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(18) 6-(2-furyl)-8-methylthio-1-(methylpropylamino) methyl-10-nitro-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(19) 8,9-dibromo-1-(diethylamino)methyl-4-methyl-6-(4-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(20) 8-chloro-6-(1-cyclopentenyl)-1-(methylethylamino) methyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(21) 1-(diethylamino)methyl-6-ethyl-8-fluoro-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(22) 8-bromo-1-(ethylpropylamino)methyl-6-propyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(23) 6-(1-cyclohexenyl)-8-nitro-4-propyl-1-pyrrolidinomethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(24) 9-chloro-6-(2-furyl)-1-pyrrolidinomethyl-8-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(25) 10-chloro-6-methyl-1-(dipropylamino)methyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(26) 6-ethyl-10-fluoro-1-(diisopropylamino)methyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(27) 8-bromo-1-propoxymethyl-6-propyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepine (I),
(28) 9-bromo-6-(1-cycloheptenyl)-4-ethyl-1-methoxymethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(29) 8-chloro-6-cyclohexyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(30) 9-bromo-6-methyl-1-propyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(31) 8,9-dibromo-6-ethyl-1-(methylthio)methyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I)
(32) 4,5-diethyl-1-(ethylthio)methyl-9-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(33) 10-chloro-6-cyclopentyl-1-(propylthio)methyl-4-ethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(34) 1-(isopropylthio)methyl-8-nitro-6-(2-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(35) 9-bromo-1-methoxymethyl-6-(4-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(36) 6-(2-pyrimidyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(37) 8-chloro-6-methyl-1-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(38) 10-fluoro-1-phenyl-6-(2-pyrryl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine (I),
(39) 1-benzyl-4-ethyl-8-fluoro-6-(2-furyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine (I),
(40) 1-benzyl-8-bromo-9-chloro-6-cyclopentyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),

(41) 9-bromo-6-cyclopentyl-1-methoxymethyl-8-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(42) 8-bromo-1-cyanomethyl-6-cyclohexyl-8-nitro-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(43) 9-bromo-6-cycloheptyl-1-nitromethyl-4-propyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(44) 8-chloro-6-isopropenyl-4-methyl-1-nitromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (I),
(45) methyl 9-chloro-4-ethyl-8-nitro-6-(4-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-carboxylate (I),
(46) methyl 8-bromo-6-(2-furyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-carboxylate (I),
(47) ethyl 8-bromo-6-(1-cyclohexenyl)-10-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-carboxylate (I),
(48) propyl 4,6-dimethyl-8-propoxy-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-carboxylate (I),
(49) propyl 4-ethyl-6-propyl-9-trifluoromethyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-carboxylate (I),
(50) isopropyl 8,10-dichloro-4-ethyl-6-(2-thienyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-carboxylate (I), etc.

I claim:

1. A compound of the formula



wherein R is selected from the group consisting of hydrogen, lower alkyl of 1 through 3 carbon atoms and lower alkoxymethyl, lower dialkylaminomethyl and lower alkylthiomethyl wherein their lower alkyl moieties are of from 1 through 3 carbon atoms; R_1 is selected from the group consisting of hydrogen, lower alkyl of 1 through 3 carbon atoms and hydroxymethyl; R_3 is selected from the group consisting of hydrogen, halogen, trifluoromethyl and nitro; and a pharmacologically acceptable acid addition salt thereof.

2. A compound of claim 1 wherein R is methyl, R_1 is hydrogen and R_3 is 8-bromo, namely, 8-bromo-1-methyl-6-(2-pyridyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

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260—239 BD, 256.4, 256.4 R, 294.8 B, 295 S, 308 R; 424—251, 263, 266, 269