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Hester, Jr.

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[54] **AMIDO AND AMINO TRIAZOLO BENZODIAZEPINES**

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[52] **U.S. Cl.** ..... **260/308 R**, 71/92, 260/247.1, 260/247.2 A, 260/247.5 B, 260/293.59, 424/248, 424/267, 424/269

[51] **Int. Cl.** **C07d 57/02**, C07d 99/02

[58] **Field of Search** ..... 260/308 R, 247.1, 260/247.5 B, 293.59, 247.2 B

[56] **References Cited**

OTHER PUBLICATIONS

Houben-Weyl, Methoden Der Organischen Chemie, Vol. 11/2, (Stuttgart, 1958), pages 20–23.

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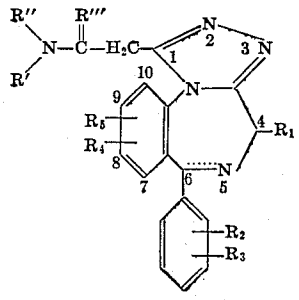
[57] **ABSTRACT**

Compounds of the formula:

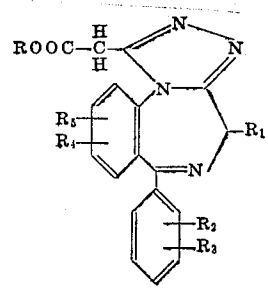


(V)

wherein R′ and R″ are hydrogen, alkyl of one to three carbon atoms, inclusive, or together

are pyrrolidino, piperidino, hexamethyleneimino, or morpholino; wherein R‴ is

or oxygen; R_1 is hydrogen or alkyl defined as above; R_2, R_3, R_4, and R_5 are selected from the group consisting of hydrogen, alkyl defined as above, halogen, nitro, cyano, trifluoromethyl, and alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, and dialkylamino, in which the carbon chain moiety is of one to three carbon atoms, inclusive, and in which the five to six nitrogen-carbon linkage is selected from the group consisting of double bonds and single bonds, with the proviso that the linkage is always a double bond whenever R‴ is oxygen; are produced from the carboxylic acid esters (I)



I

wherein R_1, R_2, R_3, R_4, and R_5 are defined as above and R is alkyl of one to three carbon atoms, inclusive.

3 Claims, No Drawings

AMIDO AND AMINO TRIAZOLO BENZODIAZEPINES

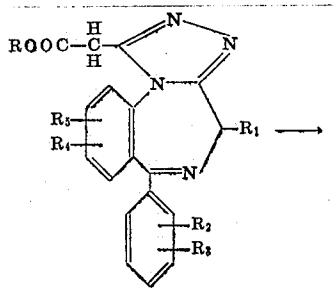
The new compounds of formula V above and the pharmacologically acceptable acid addition salts thereof have oral and parenteral sedative and tranquilizing activity and can be employed for tranquilizing mammals e.g. pets and zoo animals in transit.

BACKGROUND OF THE INVENTION

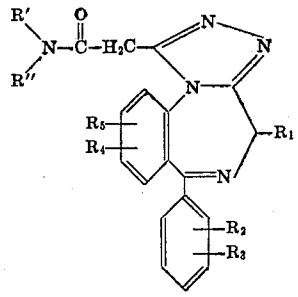
FIELD OF THE INVENTION

This invention is directed to novel organic compounds and is more specifically concerned with amidoand amino-triazolobenzodiazepines of the formulae below and a method of the production thereof.

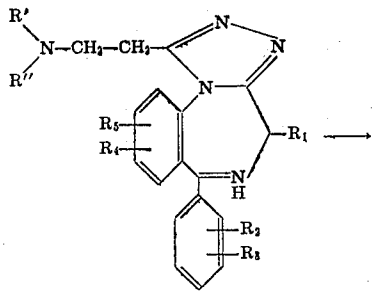
The novel compounds and the process therefor can be illustratively represented as follows:



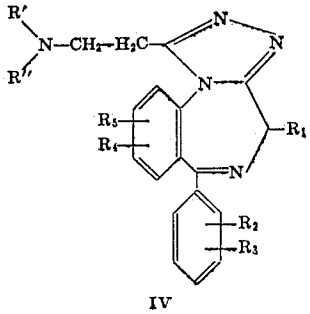
I



II



III



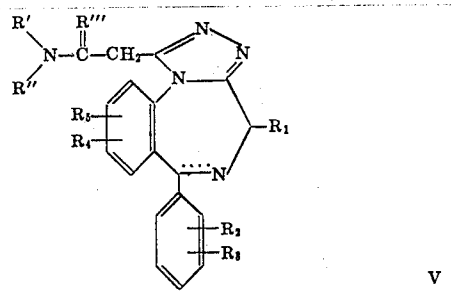
IV

wherein R′ and R″ are hydrogen, alkyl of one to three carbon atoms, inclusive, or together

are pyrrolidino, piperidino, hexamethyleneimino, and morpholino; wherein R_1 is hydrogen or alkyl defined as above; and wherein R_2, R_3, R_4, and R_5 are selected from the group consisting of hydrogen, alkyl defined as above, halogen, nitro, cyano, trifluoromethyl, and alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, and dialkylamino, in which the carbon chain moiety is of one to three carbon atoms, inclusive.

The process of this invention comprises treating an ester of formula I with ammonia or an amine at a temperature between 25°–200° C. in an organic solvent to obtain an amide of formula II; reducing the amide with borane or a metal aluminum hydride in a solvent between room temperature and the reflux temperature of the reaction mixture to obtain the amine III of the formula above and oxidizing III e.g. with manganese dioxide, ruthenium tetroxide or with diethyl azodicarboxylate to obtain the benzodiazepine of formula VI.

The active compounds of this invention II, III, and IV can be summarily represented by Formula V



V

wherein R′ and R″ are hydrogen, alkyl of one to three carbon atoms, inclusive or together

are pyrrolidino, piperidino, hexamethylenemino, and morpholino; wherein R‴ is

or oxygen; wherein R_1 is hydrogen or alkyl defined as above; and wherein R_2, R_3, R_4, and R_5 are selected from the group consisting of hydrogen, alkyl defined as above, halogen, nitro, cyano, trifluoromethyl, and alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, and dialkylamino, in which the carbon chain moiety is of one to three carbon atoms, inclusive, and the five to six nitrogen-carbon linkage can be selected from the group consisting of double bonds and single bonds, with the proviso that it is always a double bond whenever R‴ is oxygen.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Lower alkyl groups of one to three carbon atoms, inclusive, are exemplified by methyl, ethyl, propyl, and isopropyl.

The carbon chain moiety of alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, dialkylamino which is of one to three carbon atoms, inclusive, is defined as lower-alkyl of one to three carbom atoms, inclusive, as above.

The term halogen includes fluorine, chlorine, and bromine.

The novel compounds of the formula V(or II, III, and IV) including pharmacologically acceptable acid addition salts thereof, have sedative, tranquilizing and muscle relaxant effects in mammals and birds.

The pharmacologically acceptable acid addition salts of compounds of formula V (or II, III, and IV) contemplated in this invention, are the hydrochlorides, hydrobromides, hydroiodides, sulfates, phosphates, cyclohexanesulfamates, methanesulfonates and the like, prepared by reacting a compound of formula II, III, or IV with an excess of the selected pharmacologically acceptable acid.

Sedative effects of N,N-dimethyl-8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide are shown by the following tests in mice:

CHIMNEY TEST

Med. Exp. 4, [145 (1961)]: The effective intraperitoneal dosage for 50 percent of mice (ED_{50}) is 8.8 mg./kg. 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 percent 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 percent of the mice remain in the dish. The ED_{50} (intraperitoneal administration) in this test was 7.0 mg./kg.

PEDESTAL TEST

The untreated mouse leaves the 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 one minute. The ED_{50} (intraperitoneal administration) is 12.5 mg./kg.

NICOTINE ANTAGONISM

Mice in a group of 6 are injected with the test compound N,N-dimethyl-8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide. 30 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. An intraperitoneal dosage of 1.6 mg./kg. of the test compound protected 50 percent of the mice against (2) and 1.8 mg./kg. against (3).

The pharmaceutical forms of compound V (or II, III, and IV) 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 may be used as carriers or for coating purposes. Oils, e.g. coconut oil, sesame oil, safflower oil, cottonseed oil, peanut oil may be used for preparing solutions or suspensions of the active drug. Sweetening, coloring and flavoring agents may 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 V can be used in dosages of 1–20 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 shipped.

Other acid addition salts of the compounds of formula V can be made, such as the fluosilicic acid addition salts which are useful mothproofing compounds or the trichloroacetates useful as herbicides against Johnson grass, Bermuda grass, yellow foxtail, and green foxtail, and quack grass.

The starting materials of formula I of this invention, substituted or unsubstituted 6-phenyl-4H -s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl esters are produced from 6-phenyl-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetonitriles as shown in Preparation 2. The acetonitriles are produced as in preparation 1 from 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thiones [described by G. A. Archer et al., J. Org. Chem. 29, (231) 1964].

In carrying out the process of this invention a compound of formula I is reacted with aqueous ammonia or aqueous lower dialkylamine in dimethylformamide, dioxane, tetrahydrofuran or the like or with a dialkylamine, or an lower N-heterocyclicamine, preferably in a solvent, e.g. dimethylformamide, dimethylacetamide or the like, between 25°–200° C. The N-heterocyclicamines useful for these are piperidine, pyrrolidine, morpholine, hexamethyleneimine.

The product (II) obtained is recovered and purified by standard methods e.g. extraction, chromatography, and crystallization.

Compound II, in ether or tetrahydrofuran when treated with borane (B_2H_6) or lithium aluminum hydride between 25°–80° C. yields the amine of formula III which is recovered and purified by conventional means e.g. extraction, chromatography, and recrystallization.

Compound III can be oxidized in part with active manganese dioxide preferably in benzene, tetrahydrofuran or other anhydrous solvent or with ruthenium tetroxide in a solvent such as chloroform or carbontetrachloride.

Instead of manganese dioxide or ruthenium tetroxide diethyl azodicarboxylate is useful and is preferred. The temperature of this reaction is between 25°–80° C. and the time is between 1 and 18 hours. The product IV is isolated and purified by conventional means e.g. extraction, chromatography, and recrystallization.

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

PREPARATION 1

8-Chloro-6-phenyl-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetonitrile

A mixture of 1,3-dihydro-7-chloro-5-phenyl-2H-1,4-benzodiazepine-2-thione (5.72 g., 0.02 mole), cyanoacetic acid hydrazide (5.95 g., 0.06 mole) and n-butylalcohol (275 ml.) was refluxed for 7.5 hours with a slow stream of nitrogen bubbling through the mixture. The mixture was then concentrated in vacuo. The resulting residue was suspended in water and extracted with methylene chloride. The extract was dried and concentrated. The residue was chromatographed on silica gel (400 g.) with 2 percent methanol-98 percent $CHCl_3$. The product eluted from the column was crystallized from ethyl acetate-Skelly B hexanes to give 2.62 g. of 8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetonitrile of melting point 198°–201° C. Anal. calcd. for $C_{18}H_{12}ClN_5$:

C, 64.77; H, 3.63; cl, 10.62.

Found: C, 64.52; H, 3.86; Cl, 10.51.

PREPARATION 2

8-Chloro-6-phenyl-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetic acid methyl ester

A stirred mixture of 8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetonitrile (1.00 g., 0.003 mole), methanol (2 ml.) and ether (6 ml.) was cooled in a salt-ice bath and saturated with a stream of anhydrous hydrogen chloride during 15 minutes. The mixture was allowed to warm slowly to ambient temperature and stand for 18 hours; it was then poured into water. This mixture was neutralized with sodium bicarbonate and extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate and then concentrated. The residue was cyrstallized from methanol to give 0.149 g. of a by-product of melting point 184.5°–188° C. (d). The mother liquor was crystallized from methanol-ethyl acetate to give 0.126 g. of a by-product of melting point 205.5°–207.5° (d.) C. The mother liquor from this crystallization was concentrated and chromatographed on silica gel (50 g.) with 2 percent methanol-98 percent chloroform. The first compound eluted from the column was crystallized from methanol-ethyl acetate to give 0.169 g. of melting point 202.5°–203.5° C. (d.) and 0.125 g. of melting point 200.5°–202.5° C. (d.) of 8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester. The analytical sample had a melting point of 202°–203° C.

ANAL. CALCD. FOR $C_{19}H_{15}ClN_4O_2$

C, 62.21; H, 4.12; Cl, 9.67; N, 15.28.

Found:

C, 62.32; H, 4.14; Cl, 10.15; N, 15.33.

EXAMPLE 1

N,N-dimethyl-8-chloro-6-phenyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepine-1-acetamide

A suspension of 8-chloro-6-phenyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester (0.367 g., 0.001 mole) in 25 percent aqueous dimethylamine (5 ml.) and dimethylformamide (6 ml.) was treated with dimethylamine hydrochloride (81.5 mg.) and stirred under nitrogen at ambient (23°–25° C.) temperature for 18 hours. It was poured into cold water, saturated with sodium chloride and extracted with methylene dichloride. The extract was washed with a dilute sodium chloride solution, dried over anhydrous potassium carbonate and concentrated in vacuo. The resulting residue was washed successively with xylene and toluene with concentrating after each addition. The resulting material was crystallized from methanol-ethyl acetate to give 0.173 g. of N,N-dimethyl-8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide of melting point 204°–205.5° C.

ANAL. CALCD. FOR $C_{20}H_{18}ClN_{50}$:

C, 63.24; H, 4.78; Cl, 9.35; N, 18.44

Found:

C, 63.01; H, 4.83; Cl, 9.39; N, 18.41.

EXAMPLE 2

N,N-Dimethyl-8-chloro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 8-chloro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester was reacted with dimethylamine in dimethylformamide to give N,N-dimethyl-8-chloro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 3

N,N-dimethyl-8-chloro-6-(2,6-dichlorophenyl)- 4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 8-chloro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester was reacted with dimethylamine in dimethyl formamide to give N,N-dimethyl-8-chloro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 4

N,N-Dimethyl-8-chloro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 8-chloro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester was reacted with dimethylamine in dimethylformamide to give N,N-dimethyl-8-chloro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 5

N,N-Tetramethylene-4-methyl-8-nitro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 4-methyl-8-nitro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid ethyl ester was reacted with pyrrolidine in dimethylformamide to give N,N-tetramethylene-4-methyl-8-nitro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 6

N,N-Pentamethylene-7-trifluoromethyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 7-trifluoromethyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester was reacted with piperidine in dimethylformamide to give N,N-pentamethylene-7-trifluoromethyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetamide.

EXAMPLE 7

N,N-Hexamethylene-10-isopropyl-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 10-isopropyl-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid ethyl ester was re-

acted with hexamethyleneimine in dimethylformamide to give N,N-hexamethylene-10-isopropyl-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetamide.

EXAMPLE 8

4-[[9-dipropylamino-8-ethylsulfonyl-6-(p-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-yl] acetyl]morpholine

In the manner given in Example 1, 9-dipropylamino-8-ethylsulfonyl-6-(p-methoxyphenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetic acid propyl ester was reacted with morpholine in dimethylformamide to give 4-[[9-dipropylamino-8-ethylsulfonyl-7-(p-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-yl]acetyl]morpholine.

EXAMPLE 9

N,N-Dipropyl-9-ethylsulfinyl-6-(m-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 9-ethylsulfinyl-6-(m-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid ethyl ester was reacted with dipropylamine in dimethylformamide to give N,N-dipropyl-9-ethylsulfinyl-6-(m-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 10

7,8-Dicyano-10-fluoro-6-(p-isopropylsulfonyl)-phenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 7,8-dicyano-10-fluoro-(p-isopropylsulfonylphenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetic acid methyl ester was reacted with aqueous ammonium hydroxide in dioxane to give 7,8-dicyano-10-fluoro-6-(p-isopropylsulfonylphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 11

N,N-Dimethyl-7-bromo-8-diethylamino-6-(m-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetmide

In the manner given in Example 1, 7-bromo-8-diethylamino-6-(m-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester was reacted with dimethylamine in dimethylformamide to give N,N-dimethyl-7-bromo-8-diethylamino-6-(m-cyanophenyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 12

N,N-Dimethyl-4-propyl-8-bromo-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide

In the manner given in Example 1, 4-propyl-8-bromo-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetic acid methyl ester was reacted with dimethylamine in dimethylformamide to give N,N-dimethyl-4-propyl-8-bromo-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide.

EXAMPLE 13

1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine

A solution of 1.5 g. of N,N-dimethyl-8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide was slowly added to a solution of borane in tetrahydrofuran. The reaction mixture was heated to 40° C. and was kept at this temperature for 15 hours. The mixture was then evaporated in vacuo and the remaining residue was suspended in water and extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate, then evaporated to dryness and the residue recrystallized twice from ethyl acetate, providing 1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 14

1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 13, N,N-dimethyl-8-chloro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide was reduced with borane to give 1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 15

1-[2-(Dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 13, N,N-dimethyl-8-chloro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepine-1-acetamide was reduced with borane to give 1-[2-dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 16

1-[2-(Diethylamino)ethyl]-8-chloro-5,6-dihydro-6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 13, N,N-diethyl-8-chloro-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide was reduced with borane to give 1-[2-(diethylamino)ethyl]-8-chloro-5,6-dihydro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 17

1-(2-Pyrrolidinoethyl)-4-methyl-8-nitro-5,6-dihydro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 13, N,N-tetramethylene-4-8-nitro-6-(m-bromophenyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine-1-acetamide was reduced with lithium aluminum hydride instead of borane to give 1-(2-pyrrolidinoethyl)-4-methyl-8-nitro-5,6-dihydro-6-(m-bromopheny)-4H-s-triazolo [4,3-a][1,4]benzodiazepine.

EXAMPLE 18

1-(2-Piperidinoethyl)-7-5,6-dihydro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazenpine

In the manner in Example 13, N,N-pentamethylene-7-trifluoromethyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetamide was reduced with borane to give 1-(2-piperidinoethyl)-7-trifluoromethyl-5,6-dihydro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 19

1-[2-(Hexamethyleneimino)ethyl]-10-isopropyl-5,6-dihydro-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine

In the manner given in Example 13, N,N-hexamethleneimino-10-isopropyl-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetamide was reduced with borane to give 1-[2-(hexamethyleneimino)ethyl]-10-isopropyl-5,6-dihydro-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepine.

EXAMPLE 20

1-(2-morpholinoethyl)-8-ethylsulfonyl-5,6-dihydro-6-(p-methyoxyphenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepine

In the manner given in Example 13, 4-[[8-ethylsulfonyl-6-(p-methyoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepin-1-yl]acetyl]morpholine was reduced with borane to give 1-(2-morpholinoethyl)-8-ethylsulfonyl-5,6-dihydro-6-(p-methoxphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 21

1-[2-(Dipropylamino)ethyl]-9-ethylsulfinyl-5,6-dihydro-6-(m-nitrophenyl)-4H-s-triazolo[4,3a][1,4]-benzodiazepine

In the manner given in Example 13, N,N-dipropyl-9-ethylsulfinyl-6-(m-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepine-1-acetamide was reduced with borane to give 1-[2-(dipropylamino)ethyl]-9-ethylsulfinyl-5,6-dihydro-6-(m-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 22

1-[2-(dimethylamino)ethyl]-7-bromo-8-(diethylmino)-5,6-dihydro-6-(m-cyanophenyl)-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine

In the manner given in Example 13, N,N-dimethyl-7-bromo-8-(diethylamino)-6-(m-cyanophenyl)-4H-s-triazo-[4,3-a][1,4]benzodiapine-1-acetamide was reduced with borane to give 1-[2-(dimethylamino)ethyl]-7-bromo-8-(diethylamino)-5,6-dihydro-6-(m-cyanophenyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine.

EXAMPLE 23

1-[2-(diethylamino)ethyl]-4-propyl-8-brom-5,6-dihydro-6-(o-bromophenyl)-4H-s-triazolo[4,3a][1,4]-benzodiazepine

In the manner given in Example 13, N,N-diethyl-4-propyl-8-bromo-6-(o-bromophenyl)-4H-s-trizaolo[4,3-a][1,4]-benzodiazepine-1-acetamide was reduced with borane to give 1-[2-(diethylamino)ethyl]-4-propyl-8-bromo-5,6-dihydro-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 24

1-[2-(Dimethylamino)ethyl]-8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine

A stirred suspension of 1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-phenyl-4H-s-triazolo[4,3-a][1,4]-benzodiazepine and diethyl azodicarboxylate in benzene was heated to reflux and kept at this temperature for about 15 hours. The mixture was then cooled and evaporated. The residue was suspended in water and extracted with chloroform. The chloroform extracts were dried with anhydrous potassium carbonate, evaporated and the resulting residue twice crystallized from ethyl acetate to give 1-[2-(dimethylmino)ethyl]-8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 25

1-[2-(dimethylamino)ethyl]-8-chloro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-[2-(dimethylamino)ethyl]-8-chloro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 26

1-[2-(Dimethylamino)ethyl]-8-chloro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a supension of 1-[2-(dimethylamino)ethyl]-8-chloro-5,6-dihydro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-[2-(dimethylamino)ethyl]-8-chloro-6-(2,6-dichlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 27

1-[2-(diethylamino)ethyl]-8-chloro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-[2-(diethylamino)ethyl]-8-chloro-5,6-dihydro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-[2-(diethylamino)ethyl]-8-chloro-6-(2,6-difluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 28

1-(2-Pyrrolidinoethyl)-4-methyl-8-nitro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-(2-pyrrolidinoethyl)-4-methyl-8-nitro-5,6-dihydro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-(2-pyrrolidinoethyl)-4-methyl-8-nitro-6-(m-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

EXAMPLE 29

1-(2-Piperidinoethyl)-7-trifluoromethyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-(2-piperidinoethyl)-7-trifluoromethyl-5,6-dihydro-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-(2-piperidinoethyl)-7-trifluoromethyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 30

1-[2-(Hexamethyleneimino)ethyl]-10-isopropyl-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-[2-(hexamethyleneimino) ethyl]-10-isopropyl-5,6-dihydro-6-(p-methylthiophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-[2-(hexamethyleneimino)ethyl]-

10-isopropyl-6-(p-methylthio-phenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

EXAMPLE 31

1-(2-Morpholinoethyl)-8-ethylsulfonyl-6-(p-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-(2-morpholinoethyl)-8-ethylsulfonyl-5,6-dihydro-6-(p-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-(2-morpholinoethyl)-8-ethylsulfonyl-6-(p-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

EXAMPLE 32

Example 33

1-[2-(dimethylamino)ethyl]a -7-bromo-8-diethylamino-6-(m-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-[2-dimethylamino)ethyl]-7-bromo-8-diethylamino-5,6-dihydro-6-(m-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-[2-(dimethylamino)ethyl]-7-bromo-8-diethylamino-6-(m-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

EXAMPLE 34

1-[2-(Diethylamino)ethyl]-4-propyl-8-bromo-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine

In the manner given in Example 24, a suspension of 1-[2-(diethylamino)ethyl]-4-propyl-8-bromo-5,6-dihydro-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine was oxidized with diethyl azodicarboxylate to give 1-[2-(diethylamino)ethyl]-4-propyl-8-bromo-6-(o-bromophenyl)-4H-s-triazolo[4,3-a][1,4 benzodiazepine.

In the manner given in Examples 1–12, other 6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamides of of amines such as ammonia, dialkylamines, piperidine, pyrrolidine, morpholine or hexamethyleneimine are produced by reacting a starting compound of formula I above with a dialkylamine, ammonia, pyrrolidine, morpholine, piperidine, or hexamethyleneimine.

Compounds thus produced include:

N,N-dipropyl-10-chloro-6-(m-isopropylphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-diisopropyl-9-(dipropylamino)-6-[p-(dipropylamino) phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-diethyl-8-(methylsulfinyl)-6-(o-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-dimethyl-7-(ethylsulfonyl)-6-(o-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-pentamethylene-4-propyl-6-[m-(methylthio)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-tetramethylene-10-fluoro-7-chloro-6-[p-(trifluoromethyl)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-hexamethylene-7,9-diethoxy-6-(m-ethoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-diethyl-7-(propylthio)-6-(m-chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-dimethyl-8-(dimethylamino)-6-(p-fluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

4-[[4-propyl-6-(o-fluorophenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepin-1-yl]acetyl]morpholine;

4-methyl-7,10-dichloro-6-(m-isopropoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-tetramethylene-9-(dipropylamino)-6-[m-(propylthio)-phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-diethyl-7-(diisopropylamino)-6-[p-(dipropylamino)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-acetamide;

N,N-dipropyl-8-chloro-6-(3,4-dimethylphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiapine-1-acetamide;

4-[[6-(2-methyl-4-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]-benzodiazepin-1-yl]acetyl]morpholine; and the like.

In the manner given in Example 15 other N,N-dialkyl-6-phenyl-4H-S-triazolo[4,3-a][1,4]benzodiazepine-1-acetamides or the pyrrolidine, piperidine, 4-morpholine or hexamethyleneimine analogues can be reduced with borane in tetrahydrofuran to produce other 1-(2-aminoethyl)substituted compounds of formula III. Representative compounds thus obtained include:

1-[2-(diethylamino)ethyl]-10-chloro-5,6-dihydro-6-(m-isopropylphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(dipropylamino)ethyl]-9-(dipropylamino)-5,6-dihydro-6-[p-(dipropylamino)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(dimethylamino)ethyl]-8-(methylsulfinyl)-5,6-dihydro-6-(o-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-(2-morpholinoethyl)-7-(ethylsulfonyl)-5,6-dihydro-6-(o-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-(2-piperidinoethyl)-4-propyl-5,6-dihydro-6-[m-(methylthio)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(hexamethyleneimino)ethyl]-10-fluoro-7-chloro-5,6-dihydro-6-[p-(trifluoromethyl)phenyl]-4H-s-triazolo[4,3-a]-[1,4-]benzodiazepine;

1-(2-pyrrolidinoethyl)-7,9-diethoxy-5,6-dihydro-6-(m-ethoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-(2-pyrrolidinoethyl)-7,9-diethoxy-5,6-dihydro-6-(m-ethoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(diethylamino)ethyl]-7-propylthio)-5,6-dihydro-6-(m-fluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiapine;

1-[2-(dipropylamino)ethyl]-4-propyl-5,6-dihydro-6-(o-fluorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(diisopropylamino)ethyl]-4-ethyl-5,6-dihydro-6-[o-ethylthio)-phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(diethylamino)ethyl]-4-methyl-7,10-dichloro-5,6-dihydro-6-(m-isopropoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;

1-[2-(diethylamino)ethyl]-9-(dipropylamino)-5,6-dihydro-6-[m-propylthio)phenyl9 -4H-s-triazolo[4,3-a][1,4]benzodiazepine;

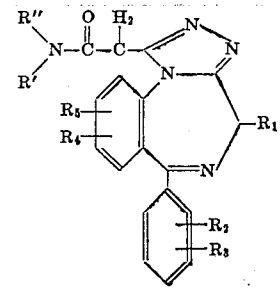
1-(2-morpholinoethyl)-7-(diisopropylamino)-5,6-dihydro-6-[p-(dipropylamino)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-piperidinoethyl]-8-chloro-5,6-dihydro-6-(3,4-dimethylphenyl)- 4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-piperidinoethyl)-5,6-dihydro-6-(2-methyl-4-methoxyphenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-pyrrolidinoethyl)-8-methylthio-5,6-dihydro -6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-pyrrolidinoethyl)-8-methoxy-5,6-dihydro-6-phenyl-4H-s-triazolo[4,3-][1,4]benzodiazepine; an the like.

In the manner given in Example 24 other 1-(2-aminoethyl) and 1-[2-(substituted amino)ethyl]-5,6-dihydro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepines (III) can be oxidized to give the corresponding 1-(2-aminoethyl) and 1-[2-(substituted amino)ethyl]-6-phenyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepines of formula IV. Representative compounds, thus obtained, include:
1-[2-(diethylamino)ethyl]-10-chloro-6-(m-isopropylphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-(dipropylamino)ethyl]-9-(dipropylamino)-6-[p-(dipropylamino)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-(dimethylamino)ethyl]-8-methylsulfinyl)-6-(o-nitrophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1(2-morpholinoethyl)-7-(ethylsulfonyl)-6-(o-cyanophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-piperidinoethyl)-4-propyl-6-[m-(methylthio)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-(hexamethyleneimino)ethyl]-10-fluoro-7-chloro-6-[p-trifluoromethyl)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-pyrrolidinoethyl)-7,9-diethoxy-6-(m-ethoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-(diisopropylamino)ethyl]-4-ethyl-6-[o-(ethylthio)-phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-(diethylamino)ethyl]-4-methyl-7,10-dichloro-6-[m-isopropoxyphenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-[2-(diethylamino)ethyl]-9-(dipropylamino)-6-[m-(propylthio)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-morpholinoethyl)-7-(diisopropylamino)-6-[p-(dipropylamino)phenyl]-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-piperidinoethyl)-8-chloro-6-(3,4-dimethylphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-pyrrolidinoethyl)-6-(2-methyl-4-methoxyphenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepine;
1-(2-pyrrolidinoethyl)-8-methylthio-6-phenyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepine.
1-(2-pyrrolidinoethyl)-8-methoxy-6-phenyl-4H-s-triazolo-[4,3-a][1,4]benzodiazepine; and the like.

The pharmacologically acceptable acid addition salts of compounds of formula V can be prepared and isolated by conventional processes, such as reacting a compound of formula V with a selected pharmacologically acceptable acid. Such acids include hydrochloric, hydrobromic, phosphoric, sulfuric, acetic, tartaric, lactic, citric, malic, maleic, methanesulfonic, benzenesulfonic, cyclohexanesulfonic acids, and the like. The reaction is conveniently performed in an organic solvent e.g. ether, dioxane, tetrahydrofuran and the salts recovered by evaporating the solvent.

I claim:

1. A compound of the formula:



wherein R′ and R″ are hydrogen, or alkyl of one to three carbon atoms, inclusive, or together

are pyrrolidino, piperidino, hexamethyleneimino, or morpholino; wherein R_1 is hydrogen or alkyl, defined as above; wherein R_2, R_3, R_4, and R_5 are selected from the group consisting of hydrogen, alkyl defined as above halogen, nitro, cyano, trifluoromethyl, and alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, and dialkylamino, in which the carbon chain moiety is of one to three carbom atoms, inclusive, and the pharmacologically acceptable acid addition salts thereof.

2. N,N-dimethyl-8-chloro-6-phenyl-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine-1-acetamide.

3. N,N-dimethyl-8-chloro-6-(o-chlorophenyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine-1-acetamide.

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