

# United States Patent [19]

Arimura et al.

[11] 3,856,797

[45] Dec. 24, 1974

[54] 8-AMINOALKYL-3-OXO-1-THIA-4,8-DIAZASPIRO(4.5)DECANES AND ANALOGS THEREOF

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[52] U.S. Cl. .... **260/293.66**, 424/246, 424/248, 424/250, 424/267, 260/243 R, 260/244 R, 260/247.5 R, 260/247.1 M, 260/247.2 A, 260/268 H, 260/268 BC, 260/293.63, 260/293.64, 260/293.65, 260/293.67, 260/293.69, 260/293.71, 260/293.78, 260/293.79, 260/293.87

[51] Int. Cl. .... **C07d 29/34**

[58] Field of Search .... **260/293.66, 243 R, 244 R, 260/293.63, 293.64, 268 BC, 247.1 M, 247.2 A**

## [56] References Cited

### UNITED STATES PATENTS

3,574,204	4/1971	Nakanishi et al. ....	260/293.66
3,577,425	5/1971	Nakanishi et al. ....	260/293.58
3,720,670	3/1973	Nakanishi et al. ....	260/293.66

3,723,442 3/1973 Nakanishi et al. .... 260/293.66

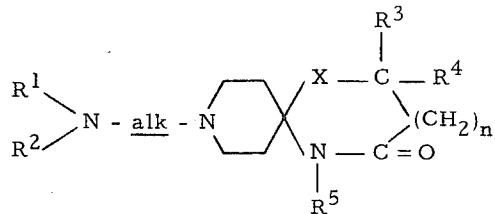
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## [57] ABSTRACT

8-Aminoalkyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decanes and analogs thereof of the formula:



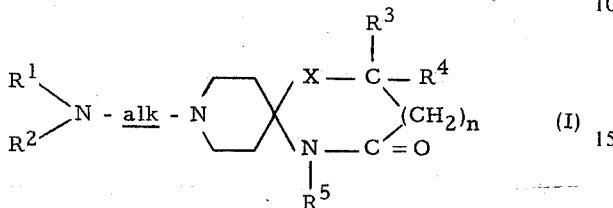
wherein X is —S—, —SO—, —SO<sub>2</sub>— or —O—; each of R<sup>1</sup> and R<sup>2</sup> is H, lower alkyl, cycloalkyl, aryl, aralkyl, furyl-lower-alkyl, pyridyl or pyridyl-lower-alkyl, or R<sup>1</sup>, R<sup>2</sup> and N form a heterocyclic ring; each of R<sup>3</sup> and R<sup>4</sup> is H, lower alkyl or aryl; R<sup>5</sup> is H, lower alkyl, aryl, aralkyl, furyl-lower-alkyl or pyridyl; alk is alkylene having 1 to 4 carbon atoms; and n is zero or 1; in which definitions the term "lower" in each occurrence means that the alkyl group or moiety has no more than 4 carbon atoms; and the pharmaceutically acceptable acid addition salts thereof are disclosed. These compounds are used in liver dysfunction.

13 Claims, No Drawings

8-AMINOALKYL-3-OXO-1-THIA-4,8-DIAZASPIRO(4,5)DECANES AND ANALOGS THEREOF

SUMMARY OF THE INVENTION

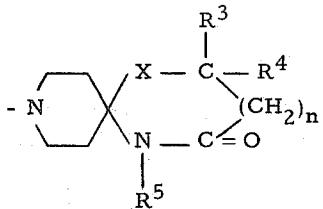
This invention relates to novel and therapeutically valuable 8-aminoalkyl-3-oxo-1-thia-4,8-diazaspiro[4,5]decanes and analogs thereof of the general formula:



and the pharmaceutically acceptable acid addition salts thereof.

In the above formula, X represents  $-\text{S}-$ ,  $-\text{SO}-$ ,  $-\text{SO}_2-$  or  $-\text{O}-$ ; each of  $R^1$  and  $R^2$  represents a hydrogen atom, a lower alkyl group (e.g., methyl, ethyl, propyl or butyl), a cycloalkyl group (e.g., cyclopentyl, cyclohexyl or cycloheptyl), an aryl group (e.g., phenyl, chlorophenyl, methoxyphenyl, tolyl or trifluoromethyl-phenyl), an aralkyl group (e.g., benzyl, phenethyl, chlorobenzyl or methoxybenzyl), a furyl-lower-alkyl group (e.g., furfuryl, 3-furylmethyl or 2-(2-furyl)ethyl), a pyridyl group (2-, 3- or 4-pyridyl) or a pyridyl-lower-alkyl group (e.g., 2-pyridylmethyl, 2-(2-pyridyl)ethyl, 3-pyridylmethyl or 2-(4-pyridyl)ethyl, or  $R^1$  and  $R^2$  together with the adjacent N atom form a heterocyclic ring (e.g., pyrrolidine, piperidine, morpholine, N'-lower-alkyl-piperazine, N'-aryl-piperazine, N'-aralkyl-piperazine or N'-(2-hydroxymethyl)piperazine); each of  $R^3$  and  $R^4$  represents a hydrogen atom, a lower alkyl group or an aryl group;  $R^5$  represents a hydrogen atom, a lower alkyl group, an aryl group, aralkyl group, a furyl-lower-alkyl group or a pyridyl group; alk represents an alkylene group having 1 to 4 carbon atoms (e.g., methylene, ethylene, propylene, trimethylene or 2-methyl-trimethylene); and  $n$  is zero or 1; in which definitions the term "lower" in each occurrence means that the alkyl group or moiety has no more than 4 carbon atoms.

Compounds having the group of the formula:

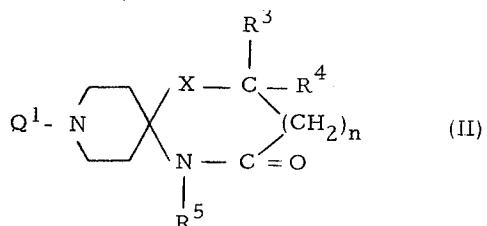


wherein each symbol is as defined above, have been disclosed, for example, in U.S. Pat. Nos. 3,574,204; 3,577,425 and 3,661,902, or British Pat. No. 1,203,430, and are said to be useful as anti-psychotic agents or vasodilators.

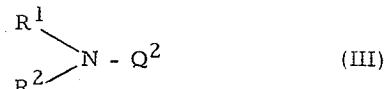
Now the present invention provides novel compounds represented by formula (I) useful as drugs to be used in liver dysfunction.

The compounds of general formula (I) can be produced by one of the following methods (i) and (ii): Method (i):

Reaction of a compound of the formula:

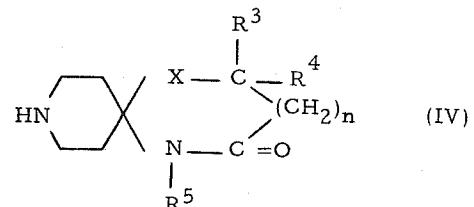


with a compound of the formula:

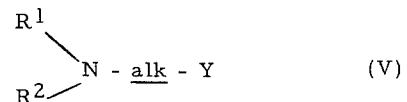


wherein one of  $Q^1$  and  $Q^2$  is a hydrogen atom and the other is a group of the formula:  $-\text{alk}-Y$  [Y being a reactive atom or group such as a halogen atom or an alkyl- or aryl-sulfonyloxy (e.g., methylsulfonyloxy or p-tolylsulfonyloxy)], and other symbols being defined as above.

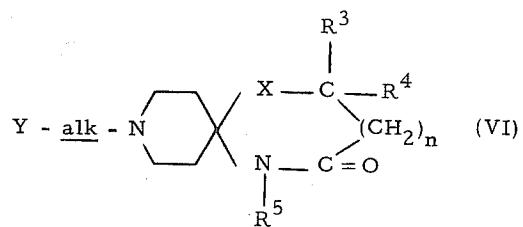
More particularly, method (i) includes two alternatives, the one comprising reacting a compound of the formula:



with a compound of the formula:



and the other comprising reacting a compound of the formula:



with a compound of the formula:



wherein each symbol is as defined above.

The reaction in method (i) is usually carried out in the presence of an inert solvent, such as methanol, ethanol, 2-propanol, acetone, methylethyl ketone, benzene, toluene, xylene, tetrahydrofuran, dioxane, ethyl acetate, dimethylformamide, dimethylsulfoxide or a mixture thereof, in the presence of an acid-acceptor,

such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, triethylamine, diethylaniline or pyridine, and if desired in the presence of a catalyst such as potassium iodide. The reaction is usually carried out at the refluxing temperature of the solvent used, but in case an aprotic polar solvent such as dimethylformamide or dimethylsulfoxide is used, a temperature of about 30° to 100°C. will suffice.

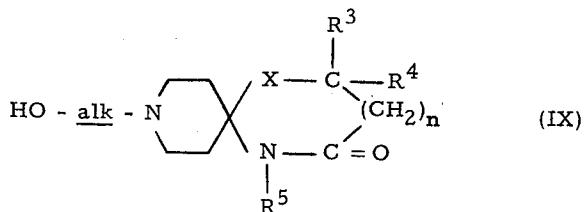
The starting compounds (IV) and (V) may be used in the form of the hydrohalide (e.g., hydrochloride or hydrobromide).

The starting compound (IV) can be prepared by the method disclosed in Belgian Pat. No. 708,051 or a modification of the said method, the subject matter of which is incorporated herein by reference.

The starting compound (VI) can be prepared, for example, (a) by reacting a compound of formula (IV) with a compound of the formula:



and then reacting the resulting compound of the formula:



with a halogenating agent (e.g., thionyl chloride, phosphorus trichloride, phosphorus tribromide, phosphorus oxychloride or phosphorus pentachloride) or an alkyl- or aryl-sulfonyl halide (e.g., methyl-, phenyl- or p-tolylsulfonyl chloride), or (b) in case Y in formula (VI) is a halogen atom, by reacting a compound of formula (IV) with a compound of the formula:

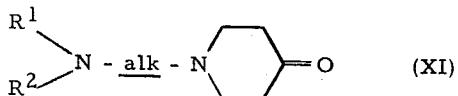


wherein each of Y<sup>1</sup> and Y<sup>2</sup> is a halogen atom.

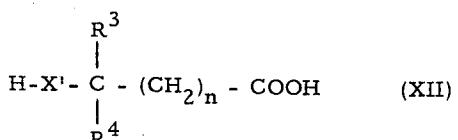
In case the amine of formula (VII) having a relatively low boiling point such as ammonia, methylamine, ethylamine, diethylamine or dimethylamine is used as a starting material, the reaction is advantageously carried out under pressure, e.g., in an autoclave, at about 50° to 120°C.

Method (ii):

This method, to be applied for the production of compounds of formula (I) wherein X is —S— or —O—, which comprises reacting a compound of the formula:



with a compound of the formula;



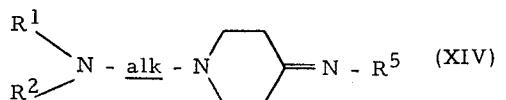
and a compound of the formula:



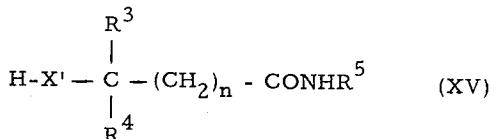
wherein X' is —S— or —O— and other symbols are as defined above.

In case R<sup>5</sup> in formula (XIII) is a hydrogen atom, it is suitable to use the compound (XIII) in the form of the carbonate, i.e., ammonium carbonate.

Method (ii) includes two modifications, the one comprising reacting a compound of formula (XI) with a compound of formula (XIII), and then reacting the resulting compound of the formula:



with a compound of formula (XII), and the other comprising reacting a compound of formula (XI) with a compound of the formula:



wherein each symbol is as defined above.

The compounds (XV) may be prepared, for example, by reacting an ester (e.g., methyl, ethyl or phenyl ester) of a compound (XII) with a compound (XIII).

The reaction in method (ii) is usually carried out in the presence of an inert solvent, such as benzene, toluene, xylene, chloroform or methylene chloride in the presence of an acid catalyst such as p-toluenesulfonic, benzenesulfonic or phosphoric acid at a refluxing temperature while removing the water formed, or in an inert solvent such as ethanol, chloroform, dioxane, tetrahydrofuran, benzene, toluene or xylene in the presence of a dehydrating agent such as calcium oxide, anhydrous magnesium sulfate, anhydrous zinc chloride or molecular sieves at a temperature range of from room temperature to an elevated temperature.

The compounds of formula (I) can be converted into the corresponding acid addition salts in a conventional manner by treating the compounds with various inorganic and organic acids, for example, hydrochloric, hydrobromic, sulfuric, nitric, oxalic, maleic, fumaric, o-(p-hydroxybenzoyl)benzoic and α-p-chlorophenoxyisobutyric acids.

The compounds of formula (I) and pharmaceutically acceptable acid addition salts thereof exhibit excellent effectiveness in treating experimental disturbances in the rat liver as shown, for example, by the following tests.

#### I. Methods

Male Wistar rats (160–240 g) were kept under standard dietary and environmental conditions. The animals were allowed access to food and water following administration of carbon tetrachloride, but were fasted for 20 hours before sacrifice. Carbon tetrachloride was dissolved in olive oil and injected intraperitoneally at a dose of 0.67 ml/kg rat body weight. Indocyanine green (ICG) at a dose of 100 mg/kg was injected intravenously 40 hours after the carbon tetrachloride administration and the animals were decapitated 15 minutes later. Serum samples were obtained for analysis. The

serum level of ICG was analyzed using the method of Cherrick et al. (Journal of Clinical Investigation, Vol. 39, pp. 592, 1960) and serum glutamic-pyruvic transaminase (S-GPT) activity was determined according to the method of Reitman et al. (American Journal of Clinical Pathology, Vol. 28, pp. 56, 1957). The test compound (0.5% methyl cellulose solution) was administered orally before and after the carbon tetrachloride injection. Animals of a comparative control group were treated with the vehicle. Protective activity 10 against liver injury was expressed as follows: reduction in ICG level and GPT activity, calculated as a percentage change from the control value: more than 60% reduction = 3, 30-60% = 2, less than 15% = 0.

## II. Results

Test	Dose	Protective Effect Against Liver Injury of Rat	
		ICG	GPT
Compound	mg/kg		
A	10	3	3
	50	3	3
B	10	2	2
	50	3	3
C	10	2	2
	50	3	3
D	50	3	3
E	50	3	3
F	50	3	3
G	50	3	3
H	50	3	3

Compounds A to H are identified below:

- A: 8-(2-Dimethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride
- B: 8-(2-Diethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate
- C: 8-(2-Dibenzylaminoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate
- D: 8-(2-Dibenzylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate
- E: 8-(2-Diethylaminoethyl)-2,2-dimethyl-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate
- F: 8-(2-Methylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride
- G: 8-(2-Aminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrobromide
- H: 8-(2-Anilinoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate

In view of various tests, including those mentioned above, the compounds of the invention represented by formula (I) and pharmaceutically acceptable acid addition salts thereof can be safely administered for the treatment of liver dysfunction, for example, acute and chronic hepatitis, liver cirrhosis, fatty liver, arteriosclerosis, and toxic hepatitis induced by ethanol, organophosphorus insecticide, chloroform, carbontetrachloride and so on, in the form of a pharmaceutical preparation with a suitable and conventional pharmaceutically acceptable inert carrier, without adversely affecting the patients.

The pharmaceutical preparations can take any conventional form such as tablets, capsules, powders or in-

jections. For example, tablets, each containing 10 mg of an active compound are prepared from the following compositions:

Compound (I) or its salt	10 mg
Lactose	60.5
Microcrystalline Cellulose	7
Cornstarch	19
Methylcellulose	0.8
Talc	2
Magnesium Stearate	0.7
	100 mg

The daily dose of compound (I) or a salt thereof for human adults usually ranges from about 60 mg to 120 mg, i.e., 6 to 12 tablets, each tablet containing 10 mg of the compound (I), in single or multiple dose, but it 15 may vary depending upon the age, body weight, and/or severity of the conditions to be treated as well as the response to the medication.

The present invention will be better understood from the following examples, which are merely illustrative 20 and not limitative thereof.

## EXAMPLE 1

A mixture of 100 g of 4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane hydrobromide, 25 46 g of 2-dimethylaminoethyl chloride hydrochloride, 130 g of sodium carbonate, 1 g of potassium iodide, 400 ml of dimethylformamide and 500 ml of toluence is stirred at room temperature for 1 hour and then refluxed for 13 hours. After cooling, the insoluble matter 30 is filtered off, and the filtrate is concentrated under reduced pressure. Water is added to the residue, and the resulting aqueous mixture is extracted with ethyl acetate. The extract is washed with an aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated. The crude product is recrystallized from isopropyl ether to give 70 g of 8-(2-dimethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane as white crystals, melting at 128°C. The corresponding dihydrochloride 40 shows a melting point of 272°C with decomposition and the maleate shows that of 226°C with decomposition.

## EXAMPLE 2

5.7 g of 2-diethylaminoethyl chloride is added to a 45 suspension of 6.9 g of 3-oxo-1-thia-4,8-diazaspiro[4.5]decane and 10 g of potassium carbonate in 100 ml of ethanol, and the resulting mixture is refluxed with stirring for 20 hours. Then the insoluble matter is filtered off, and the filtrate is concentrated 50 under reduced pressure. To the pale brown residue is added ethanolic hydrochloric acid. The white crystals precipitated are collected by filtration and recrystallized twice with methanol to give 3.8 g of 8-(2-diethylaminoethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride as white crystals, melting at 272°-274°C. with decomposition.

## EXAMPLE 3

7.5 g of 2-dibenzylaminoethyl chloride is added to a 60 suspension 8.2 g of 2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane hydrobromide and 15 g of potassium carbonate in a mixture of 80 ml of dimethylformamide and 80 ml of ethanol, and the resulting mixture is refluxed with stirring for 12 hours. After cooling to room temperature, the insoluble matter is filtered off, and the filtrate is concentrated under reduced pressure. The red-brown residue is dissolved in chloroform, and the solution is washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in acetone, and to the so-

lution is added a solution of 3 g of maleic acid in 100 ml of acetone. The precipitated crystals are collected by filtration and recrystallized from aqueous ethanol to give 4.5 g of 8-(2-dibenzylaminoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate, melting at 204°-205°C.

#### EXAMPLE 4

A mixture of 11 g of 4-p-chlorophenyl-8-(3-chloropropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, 5.5 g of cyclohexylamine, 10 g of sodium carbonate, 60 ml of dimethylformamide and 100 ml of toluene is refluxed with stirring for 13 hours. While it is warm the reaction mixture is filtered, and the filtrate is concentrated under reduced pressure. The white solid is washed with water and recrystallized from ethanol to give 8.5 g of 4-p-chlorophenyl-8-(3-cyclohexylaminopropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane as white crystals, melting at 173°C. The corresponding dimaleate shows a melting point of 223°C. with decomposition.

#### EXAMPLE 5

A mixture of 13.7 g of 8-(3-chloropropyl)-3-oxo-4-m-trifluoromethylphenyl-1-thia-4,8-diazaspiro[4.5]decane, 4 g of pyrrolidone, 10 g of sodium carbonate, 50 ml of dimethylformamide and 80 ml of toluene is refluxed with stirring for 15 hours. After cooling, the insoluble matter is filtered off, and the filtrate is concentrated under reduced pressure. The residue is dissolved in toluene, and the solution is washed three times with water, dried over magnesium sulfate and concentrated. The light brown solid is recrystallized twice with isopropyl ether to give 8 g of 8-(3-pyrrolidino-propyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane as white crystals, melting at 143°C. The corresponding dimaleate shows a melting point of 226°C. with decomposition.

#### EXAMPLE 6

A solution of 17.3 g of 4-p-chlorophenyl-8-(2-chloroethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane and 12 g of diethylamine in 150 ml of ethanol is heated at 120°C. in an autoclave for 6 hours. After cooling, the solvent is removed under reduced pressure, and the residue is dissolved in chloroform. The solution is washed twice with water, dried over magnesium sulfate and concentrated. The remaining solid is recrystallized from 2-propanol to give 11 g of 4-p-chlorophenyl-8-(2-diethylaminoethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane as white crystals, melting at 106°-107°C. The corresponding dimaleate shows a melting point of 192°C.

#### EXAMPLE 7

A mixture of 18.4 g of 1-(3-dimethylaminopropyl)-4-oxopiperidine, 14.5 g of ammonium carbonate, 11 g of thioglycollic acid and 400 ml of benzene is refluxed with stirring for 15 hours in a flask provided with a water-removing apparatus. After cooling to room temperature, about 300 ml of ethyl acetate is added to the reaction mixture and the solution is washed with a 5% aqueous sodium hydrogen carbonate solution and then a saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The brown residue is dissolved in a small amount of ethanol, and ethanolic hydrochloric acid is

added while cooling. The precipitated crystals are collected by filtration and recrystallized twice with methanol to give 14 g of 8-(3-dimethylaminopropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride as white crystals, melting at above 300°C.

#### EXAMPLE 8

A solution of 17 g of 1-(2-dimethylaminoethyl)-4-oxopiperidine, 13 g of p-chloroaniline and 0.5 g of p-toluenesulfonic acid in 400 ml of toluene is refluxed with stirring for 10 hours in a flask provided with a water-removing apparatus. After cooling to room temperature, 11 g of thioglycollic acid is added, and the resulting solution is refluxed with stirring for 8 hours. After cooling to room temperature, about 300 ml of ethyl acetate is added to the reaction mixture and the solution is washed with a 5% aqueous sodium hydrogen carbonate solution and then a saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is dissolved in a small amount of ethanol, and ethanolic hydrochloric acid is added while cooling. The precipitated crystals are collected by filtration and recrystallized twice with methanol to give 10 g of 8-(2-dimethylaminoethyl)-4-p-chlorophenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride as white crystals, melting at 269°-271°C with decomposition.

#### EXAMPLE 9

A mixture of 10.7 g of 1-(2-dibenzylaminoethyl)-4-oxopiperidine, 4.0 g of ammonium carbonate, 5.7 g of thiomandelic acid and 400 ml of benzene is refluxed with stirring for 15 hours in a flask provided with a water-removing apparatus. After cooling to room temperature, about 300 ml of chloroform is added to the reaction mixture, and the resulting mixture is washed with a 5% sodium hydrogen carbonate solution and then a saturated sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The brown residue is dissolved in acetone, and to the solution is added a solution of 4 g of maleic acid in 100 ml of acetone. The precipitated crystals are collected by filtration and recrystallized from aqueous ethanol to give 7.6 g of 8-(2-dibenzylaminoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate, melting at 204°-205°C.

#### EXAMPLE 10

A mixture of 10.8 g of 1-(2-dibenzylaminoethyl)-4-oxopiperidine, 3.0 g of lactamide, 0.5 g of p-toluenesulfonic acid and 150 ml of toluene is refluxed with stirring for 15 hours in a flask provided with a water-removing apparatus. After cooling to room temperature, the reaction mixture is washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The brown residue is dissolved in acetone, and to the solution is added a solution of 7.6 g of maleic acid in 100 ml of acetone. The precipitated crystals are collected by filtration and recrystallized from 2-propanol to give 7.0 g of 8-(2-dibenzylaminoethyl)-2-methyl-3-oxo-4,8-diazaspiro[4.5]decane dimaleate, melting at 144°-145°C. The free base product shows a melting point of 109°-110°C.

Using the procedure set forth in the above example, but substituting equivalent amounts of the appropriate

starting materials, the following compounds are also produced:

1. 8-(2-aminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrobromide, melting at 199°-200°C with decomposition 5
2. 8-(2-aminoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 184°-185°C
3. 8-(2-methylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrobromide, melting at 261°-262°C with decomposition 10
4. 8-(2-anilinoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate, melting at 201°-203°C with decomposition 15
5. 8-(3-anilinopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 83°-85°C: its dimaleate, melting at 186°C with decomposition 20
6. 8-(2-anilinoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 169°C: its maleate, melting at 201°C with decomposition
7. 8-(2-p-chloroanilinoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 68°-69°C: its maleate, melting at 201°C with decomposition 25
8. 8-(2-benzylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 205°C with decomposition 30
9. 8-[2-(2-(2-pyridyl)ethylamino)ethyl]-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 204°C with decomposition 35
10. 8-(3-furfurylaminopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate melting at 188°C with decomposition 40
11. 9-(3-dimethylaminopropyl)-4-oxo-1-thia-5,9-diazaspiro[5.5]undecane dimaleate, melting at 205°C with decomposition
12. 8-(2-diethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride, melting at 257°C with decomposition: its dimaleate, melting at 211°-212°C with decomposition: its di(α-p-chlorophenoxyisobutyrate), melting at 88°-90°C 45
13. 8-(3-diethylaminopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 217°C with decomposition
14. 4-benzyl-8-(2-diethylaminoethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]-decane dimaleate, melting at 183°C with decomposition 55
15. 4-furfuryl-8-(2-diethylaminoethyl)-3-oxo-1-thia-4,8-diazaspiro-[4.5]decane dimaleate, melting at 146°C
16. 8-(2-diethylaminoethyl)-4-(2-pyridyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 168°C 60
17. 8-(3-diethylaminopropyl)-4-p-tolyl-3-oxo-1-thia-4,8-diazaspiro-[4.5]decane dimaleate, melting at 207°-208°C with decomposition 65
18. 8-(2-diethylaminoethyl)-4-p-methoxyphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydro-

chloride, melting at 236°-239°C with decomposition

19. 8-(2-diethylaminoethyl)-2-phenyl-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 139°-140°C
20. 8-(2-diethylaminoethyl)-2-methyl-4-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 139°-140°C
21. 8-(2-diethylaminoethyl)-2-methyl-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 165°C
22. 8-(2-diethylaminoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 183°-185°C
23. 4-p-chlorophenyl-8-(2-diethylaminoethyl)-2,2-diphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 148°C: its dimaleate, melting at 151°-152°C
24. 8-(2-diethylaminoethyl)-2,2-dimethyl-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 153°C
25. 8-(3-diphenylaminopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate, melting at 211°C with decomposition
26. 8-(3-N-methylanilinopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane maleate, melting at 208°C with decomposition
27. 8-(3-N-methylanilinopropyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro-[4.5]decane, melting at 113°-115°C: its maleate, melting at 200°C with decomposition
28. 8-(3-dicyclohexylaminopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 145°C
29. 8-(2-dibenzylaminoethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 178°-179°C
30. 8-(2-dibenzylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 105°C: its maleate, melting at 212°C with decomposition
31. 8-(2-dibenzylaminoethyl)-2-phenyl-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane o-(p-hydroxybenzoyl) benzoate, melting at 146°-147°C
32. 8-(2-diethylaminoethyl)-4-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane 1-oxide dimaleate, melting at 134°C
33. 8-(2-diethylaminoethyl)-2-methyl-4-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane 1,1-dioxide dimaleate, melting at 161°C
34. 8-(2-diethylaminoethyl)-3-oxo-1-oxa-4,8-diazaspiro[4.5]decane dimaleate, melting at 164°-165°C
35. 8-(2-diethylaminoethyl)-2,2-dimethyl-3-oxo-1-oxa-4,8-diazaspiro[4.5]decane dimaleate, melting at 182°-183°C
36. 8-(2-dibenzylaminoethyl)-2-methyl-3-oxo-1-oxa-4,8-diazaspiro[4.5]decane, melting at 109°-110°C: its dimaleate, melting at 144°-145°C
37. 8-(2-dibenzylaminoethyl)-2-phenyl-3-oxo-1-oxa-4,8-diazaspiro[4.5]decane maleate, melting at 195°-196°C

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38. 8-(2-dicyclohexylaminoethyl)-2-methyl-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 155°-158°C

39. 8-(3-piperidinopropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride, melting at 264°C with decomposition

40. 8-(2-piperidinoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane, melting at 174°C: its dihydrochloride, melting at 287°C with decomposition

41. 8-(2-piperidinoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dihydrochloride, melting at above 290°C

42. 8-(3-morpholinopropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 194°C

43. 4-ethyl-8-[3-(4-methyl-1-piperazinyl)propyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decane trimaleate, melting at 189°C

44. 8-[3-(4-phenyl-1-piperazinyl)propyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 202°C

45. 2-methyl-2-phenyl-8-(2-piperidinoethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 204°-205°C

46. 8-(2-morpholinoethyl)-2,2-diphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 207°-208°C

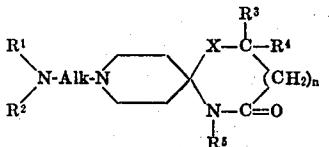
47. 2-phenyl-8-[3-(4-m-trifluoromethylphenyl-1-piperazinyl)propyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decane dimaleate, melting at 204°-205°C

48. 8-(2-diethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane 1,1-dioxide dimaleate, melting at 137°-138°C

Although the present invention has been adequately discussed in the foregoing specification and examples included therein, one readily recognizes that various changes and modifications may be made without departing from the spirit and scope thereof.

What is claimed is:

1. A compound of the formula:



wherein X is a member selected from the group consisting of  $-S-$ ,  $-SO-$ ,  $-SO_2-$  and  $-O-$ ; each of R<sup>1</sup> and R<sup>2</sup> is a member selected from the group consisting of a hydrogen atom, a lower alkyl group, a cyclohexyl group, a phenyl group, a chlorophenyl group, a benzyl

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group, a furyl-lower-alkyl group, a pyridyl group and a pyridyl-lower-alkyl group, or R<sup>1</sup> and R<sup>2</sup> together with the adjacent N atom form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine, morpholine, N'-methylpiperazine, N'-phenylpiperazine and N'-m-trifluoromethylphenylpiperazine; each of R<sup>3</sup> and R<sup>4</sup> is a member selected from the group consisting of a hydrogen atom, a lower alkyl group and a phenyl group; R<sup>5</sup> is a member selected from the group consisting of a hydrogen atom, a lower alkyl group, a phenyl group, a chlorophenyl group, a methoxyphenyl group, a tolyl group, a trifluoromethylphenyl group, a benzyl group, a furyl-lower-alkyl group and a pyridyl group; alk is an alkylene group having 1 to 4 carbon atoms; and n is a member selected from the group consisting of zero and 1; in which definitions the term "lower" in each occurrence means that the alkyl group or moiety recited has no more than 4 carbon atoms; or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of claim 1: 8-(2-dimethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

3. The compound of claim 1: 4-p-chlorophenyl-8-(3-cyclohexylaminopropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

4. The compound of claim 1: 4-p-chlorophenyl-8-(3-cyclohexylaminopropyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

5. The compound of claim 1: 4-p-chlorophenyl-8-(2-diethylaminoethyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

6. The compound of claim 1: 8-(2-aminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

35 7. The compound of claim 1: 8-(2-methylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

8. The compound of claim 1: 8-(2-anilinoethyl)-2-phenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

40 9. The compound of claim 1: 8-(3-furylaminopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

10. The compound of claim 1: 8-(2-diethylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

45 11. The compound of claim 1: 8-(3-diethylaminopropyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

12. The compound of claim 1: 8-(2-diethylaminoethyl)-2,2-dimethyl-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

13. The compound of claim 1: 8-(2-dibenzylaminoethyl)-4-m-trifluoromethylphenyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decane.

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