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THIENO-[2,3-e][1,4]DIAZEPIN-2-ONES

Michio Nakanishi, Oita, and Kazuhiko Araki, Tetsuya Tahara, and Masami Shiroki, Fukuoka, Japan, assignors to Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan

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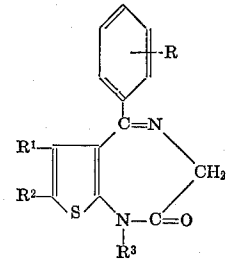
U.S. Cl. 260—239.3 B 5 Claims

ABSTRACT OF THE DISCLOSURE

Thieno-[2,3-e][1,4]diazepin-2-ones of the formula:

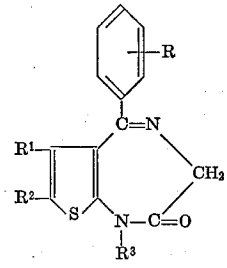


wherein each of R^1 and R^2 is a member selected from the group consisting of H and a lower alkyl group of from 1 to 4 carbon atoms, and wherein R^1 and R^2 may also combine to form a member selected from the group consisting of trimethylene and pentamethylene; R^3 is a member selected from the group consisting of H and a lower alkyl group of from 1 to 4 carbon atoms; and R is a member selected from the group consisting of H, a halogen atom, CF_3 and a lower alkoxy group of from 1 to 4 carbon atoms, providing that R does not represent H when each of R^1 and R^2 is a member selected from the group consisting of H and a lower alkyl group of from 1 to 4 carbon atoms; and the pharmaceutically acceptable acid addition salts thereof, and process for preparing same.

The compounds encompassed by the above formula exhibit pharmacological activity in narcosis potentiation, suppression of fighting behaviour and anti-convulsant activity.

SUMMARY OF THE INVENTION

The present invention relates to novel and therapeutically valuable thieno-[2,3-e][1,4]diazepin-2-ones of the formula:



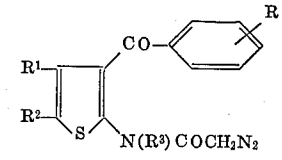
(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein each of R^1 and R^2 is H or a lower alkyl group of from 1 to 4 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tertiary butyl) or R^1 and R^2 combined may form trimethylene or pentamethylene; R^3 is H or a lower alkyl group of from 1 to 4 carbon atoms; and R is H, a halogen atom (e.g., F, Cl or Br), CF_3 or a lower alkoxy group of from 1 to 4 carbon atoms, providing that R does not represent H when each of R^1 and R^2 is H or a lower alkyl group of from 1 to 4 carbon atoms.

DETAILED DESCRIPTION OF THE INVENTION

The compounds (I) can be produced by the following methods:

(i) By condensation of a compound of the formula:

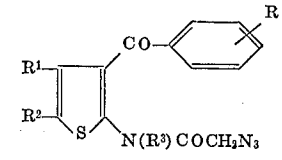


(II)

or a salt thereof such as hydrobromide or hydrochloride, wherein R, R^1, R^2 and R^3 are as defined above.

The reaction is usually carried out in a solvent such as benzene, toluene, xylene, chloroform, tetrahydrofuran, dimethylformamide or pyridine, at an elevated temperature and preferably at refluxing temperature. It is also preferred that the water formed be continuously removed azeotropically.

(ii) By reaction of a compound of the formula:

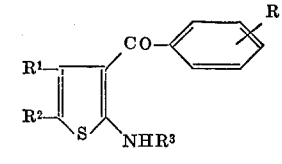


(III)

with hydrazine, wherein R, R^1, R^2 and R^3 are as defined above.

The reaction is usually carried out in a solvent such as methanol, ethanol, benzene, toluene, xylene, chloroform, methylene chloride, tetrahydrofuran, ether or dimethylformamide at a temperature of from room temperature to an elevated temperature. If desired, metal catalyst, such as palladium, platinum or nickel dispersed on a carrier such as activated charcoal, diatomaceous earth, silica gel or glass, may be employed for the purpose of accelerating the reaction.

(iii) By reaction of a compound of the formula:



(IV)

with a compound of the formula

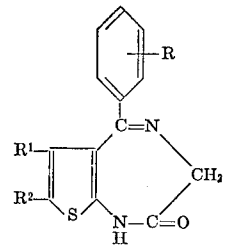
$$H_2NCH_2COOR^4 \quad (V)$$

or a salt thereof such as hydrochloride, wherein R^4 is a lower alkyl group and R, R^1, R^2, and R^3 are as defined above.

The reaction is usually carried out in a solvent such as benzene, toluene, chloroform, tetrahydrofuran, dimethylformamide or pyridine at an elevated temperature, preferably at refluxing temperature, preferably the water or alkanol formed being removed continuously.

The compounds (I) where R^3 is a lower alkyl group are also produced by the following method:

(iv) By reaction of a compound of the formula:



(I')

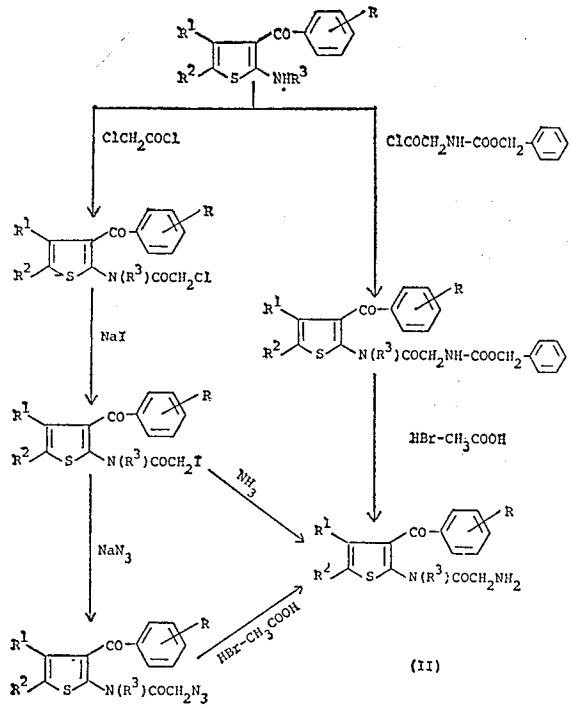
with a compound of the formula

$$R^3—X \qquad (VI)$$

wherein X is a reactive atom or group (e.g., halogen, methylsufonyloxy, p-tolylsulfonyloxy or sulfuric acid residue) and R, R^1, R^2 and R^3 are as defined above.

The reaction is usually carried out in a solvent first by converting a compound (I') into an alkali metal salt with a metalating agent, such as an alkali metal (Li, Na or K) or an alkali metal compound (hydride, alkoxide or amide of an alkali metal), and then reacting the alkali metal salt with compound (VI), at a temperature of from room temperature to refluxing temperature. The solvent employed is, for example, methanol, ethanol, benzene, xylene, tetrahydrofuran or dimethylformamide.

The starting compounds (II) and (III) are new compounds and can be produced, for example, by the following methods:



(III)

Specific examples of the preparation of starting compounds (II) and (III) are as follows:

(1) Preparation of Starting Compounds (III)

(a) To a solution of 8.5 g. of 2-amino-3-benzoyl-5,6-dihydro-4H-[1]cyclopentathiophene in 100 ml. of chloroform is added, under ice cooling, 8.3 g. of N-benzyloxycarbonylglycyl chloride, and the resulting mixture is allowed to stand in an icebox overnight. The solvent is distilled off and the crude crystals thus obtained are recrystallized from ethanol to give pale yellow crystalline 2-benzyloxycarbonylacetamido-3-benzoyl - 5,6 - dihydro-4H-[1]cyclopentathiophene, melting at 114–115° C., in 80% yield.

To 12 g. of benzyloxycarbonylacetamido-3-benzoyl-5,6-dihydro-4H-[1]cyclopentathiophene is added 30 ml. of a 20% solution of hydrogen bromide in acetic acid. The resulting mixture is stirred at room temperature, and 200 ml. of isopropyl ether is added. The crystals thus obtained are collected by filtration, washed with three 50 ml. portions of isopropyl ether, and 50 ml. of water is added. The aqueous solution is made alkaline with sodium hydrogen carbonate and extracted with chloroform. The extract is dried over sodium sulfate, the solvent is distilled off, and the crude crystals thus obtained are recrystallized from ethanol to give pale yellow crystalline 2-aminoacetamido - 3 - benzoyl-5,6-dihydro-4H-[1]cyclopentathiophene, melting at 130–131° C., in 79% yield.

(b) Ammonia gas is introduced under ice cooling to a solution of 20 g. of 2-iodoacetamido-3-o-chlorobenzoyl-5-ethylthiophene in 50 ml. of dichloromethane and 5 ml. of methanol. After the introduction of ammonia gas for 2 hours, the solution is stirred at room temperature for 2 hours to complete the reaction. The reaction mixture is washed with ice water and then with a saturated sodium hydrogen carbonate solution, dried over sodium sulfate, and concentrated under reduced pressure. The crystallization takes place on adding ethanol to the residue. The crystals are collected by filtration and washed with a small amount of ethanol to give 11.7 g. of almost pure 2-aminoacetamido-3-o-chlorobenzoyl-5-ethylthiophene, melting at 146–148° C.

(c) 2-azidoacetamido-3-o-chlorobenzoyl - 5 - ethylthiophene (5 g.) is added to 50 ml. of a 30% solution of hydrogen bromide in acetic acid, and the resulting mixture is shaken at room temperature for 1 hour. After the evolution of nitrogen gas ceases, isopropyl ether is added to the reaction mixture. The orange-colored gelatin-like substance thus precipitated is collected by decantation, isopropyl ether is added again, and the mixture is mixed well. The substance gradually solidifies. The solid is collected by filtration, washed several times with isopropyl ether, and dissolved in 50 ml. of chloroform. 5 g. of triethylamine is added, the resulting solution is allowed to stand at room temperature for 2 hours, washed with water and dried over magnesium sulfate. The chloroform is distilled off under reduced pressure to give white crystalline 2-aminoacetamido-3-o-chlorobenzoyl - 5 - ethylthiophene melting at 146–148° C. (from ethanol).

(2) Preparation of Starting Compound (III)

To a solution of 2.5 g. of 2-iodoacetamido-3-o-methoxybenzoyl-5-ethylthiophene in 15 ml. of dimethylformamide is added, with stirring, 0.42 g. of sodium azide, and the resulting mixture is stirred at 60° C. for 30 minutes. After the reaction, 20 ml. of ice water is added dropwise to the reaction mixture and the entire mixture is cooled to room temperature. The red-brown gelatin-like substance thus obtained is treated with ligroin to give white crystalline 2-azidoacetamido-3-o-methoxybenzoyl - 5 - ethylthiophene, melting at 83–84° C.

The compounds of formula (I) can be converted into the corresponding acid addition salts in a conventional manner by treatment with various inorganic and organic acids, for example, hydrochloric, hydrobromic, nitric, sulfuric, phosphoric, p-toluenesulfonic, citric, maleic, fumaric, succinic, formic, acetic and tartaric acid.

The compound of formula (I) and pharmaceutically acceptable acid addition salts thereof have excellent pharmacological activities in narcosis potentiation, suppression of fighting behavior and anticonvulsant effect as shown, for example, by the following tests.

(I) Narcosis Potentiation

The influence of 30 minutes pretreatment with the test compound on the action of 40 mg./kg. (subnarcotic dose) of hexobarbital was investigated by using eight groups each of 6 male mice. The effect of narcosis potentiation by the test compound was determined by the disappearance of righting reflex lasting above 30 seconds. Righting reflex was examined at 15 and 30 minutes after the administration of hexobarbital. When no reflex was observed at either time, the rate of narcosis potentiation was evaluated as 100%, and PD_{50} (50% potentiation dose) of the test compound was determined graphically.

(II) Suppression of Fighting Behavior

Fighting epoxides were produced in mice by the method described by Tedeschi et al. in The Journal of Pharmacology and Experimental Therapeutics, Vol. 125, p. 28 ff. (1959). Eight groups of 8 female mice (4 pairs) were given the test compound orally 60 minutes prior to receiving an electric foot-shock for 3 minutes with 530 volts interrupted direct current, 1.3 milliamperes, 10 cycles per second. Those exhibiting 3 fighting episodes or less within 3 minutes were deemed to be suppressed by the test compound. The control mice (81 pairs) had shown the fighting episodes of 8.7 times on the average under the same conditions. The ED_{50}, the dose required to suppress 50% of fighting pairs, was determined graphically.

(III) Anticonvulsant Effect

Pentylenetetrazol (150 mg./kg.) was administered subcutaneously to eight groups each consisting of 6 mice, 15 minutes after the intraperitoneal administration of the test compound. The number of dead mice were counted within 3 hours after the administration of pentylenetetrazol, and then the ED_{50}, the dose required to suppress the lethal rate to 50%, was determined graphically.

Results

Compound:	Narcosis Potentiation, PD_{50} mg./kg.
A	1.25
B	1.9
C	0.9
D	2.5

Compound:	Suppression of Fighting Behavior, ED_{50}, mg./kg.
A	5
B	3.7
C	15
D	30

Compound:	Anticonvulant Effect ED_{50} mg./kg.
A	1.9
B	0.2
C	0.9
D	0.9

The compounds A–D above are shown below:

A: 5-o-chlorophenyl-7-ethyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin-2-one

B: 5 - o - chlorophenyl-7-ethyl-1-methyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin-2-one

C: 5 - o - chlorophenyl-7-methyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin-2-one

D: 5 - o - chlorophenyl - 1,7-dimethyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin-2-one

In view of the various tests including those mentioned above, the compounds of the invention represented by formula (I) and their pharmaceutically acceptable acid addition salts thereof can be administered safely as minor tranquilizers for the treatment of neurosis, anxiety, tension and depressive states, in the form of a pharmaceutical preparation with a suitable and conventional carrier or adjuvant, administered orally, without harm to the patients.

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

Formulation Example

5 mg. and 10 mg. tablets are prepared from the following compositions:

	5 mg. tablet	10 mg. tablet
Compound (I), mg	5.0	10.0
Lactose, mg	62.3	57.3
Corn starch, mg	25.0	25.0
Microcrystalline cellulose, mg	6.0	6.0
Methyl cellulose, mg	1.0	1.0
Magnesium stearate, mg	0.7	0.7
Total, mg	100.0	100.0

1% and 10% powders are prepared from the following compositions:

	1% powder	10% powder
Compound (I), percent	1.0	10.0
Lactose, percent	88.0	79.0
Microcrystalline cellulose, percent	10.0	10.0
Methyl cellulose, percent	1.0	1.0
Total	100.0	100.0

The oral daily dose of Compound (I) or a salt thereof for human adults usually ranges from about 10 to 60 milligrams, in single or multiple dose.

The present invention will be better understood from the following examples which are merely intended to be illustrative and not limitative of the present invention.

EXAMPLE 1

A solution of 7.5 g. of 2 - aminoacetamido-3-benzoyl-5,6-dihydro - 4H - [1]cyclopentathiophene in 50 ml. of pyridine, 1.5 g. of acetic acid and 15 ml. of benzene is refluxed for 3 hours in a flask provided with a water-removing adaptor. The solvent is distilled off, water is added to the residue, the solution is made alkaline with sodium hydrogen carbonate and extracted with chloroform. The chloroform layer is dried over sodium sulfate, the chloroform is distilled off, and the crude crystals thus obtained are recrystallized from ethanol to give pale yellow crystalline 5 - phenyl - 1,2,7,8 - tetrahydro-3H,6H-[1]cyclopentathieno - [2,3-e][1,4]diazepin - 2 - one, melting at 243° C. with decomposition, in 73% yield.

EXAMPLE 2

To a solution of 10 g. of 2-aminoacetamido-3-o-chlorobenzoyl-5-ethylthiophene in 50 ml. of pyridine are added 20 ml. of benzene and 1.9 g. of acetic acid. The resulting mixture is refluxed with stirring for 10 hours in a flask provided with a water-removing adaptor. The reaction mixture is concentrated, and the residue is extracted with chloroform. The chloroform layer is washed with water and then with a sodium hydrogen carbonate solution, dried over magnesium sulfate. The chloroform is distilled off under reduced pressure, and toluene is added to the residue. Thus is precipitated white crystalline 5-o-chlorophenyl - 7 - ethyl - 1,2 - dihydro-3H-thieno-[1,3-e]-[1,4]diazepin - 2 - one, melting at 204–206° C. (from a mixture of toluene and ethanol).

EXAMPLE 3

To a solution of 4 g. of 2 - azidoacetamido - 3-o-methoxybenzoyl - 5 - ethylthiophene in 60 ml. of ethanol are added 2 g. of 5% palladium charcoal and then a solution of 0.3 g. of hydrazine hydrate in 10 ml. of ethanol with stirring. The resulting mixture is stirred at room temperature for 2 hours (nitrogen gas develops vigorously) and then at 50° C. for further 30 minutes. The insoluble catalyst is then filtered off, and the filtrate is concentrated under reduced pressure. The oily residue is crystallized

from hexane to give pale yellow crystalline 5-o-methoxyphenyl - 7 - ethyl - 1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin-2-one, melting at 168–169° C. (from a mixture of ethanol and hexane).

EXAMPLE 4

To a solution of 8.3 g. of 2-amino-3-o-chlorobenzoyl-5-ethylthiophene in 40 ml. of pyridine is added 13 g. of ethyl glycinate hydrochloride, and the resulting mixture is refluxed with stirring for 20 hours. The pyridine is then distilled off under reduced pressure, and the residue is extacted with chloroform. The chloroform layer is washed well with water and dried over magnesium sulfate, and the chloroform is distilled off under reduced pressure. The red-brown oily residue is purified by silica gel-chromatography using chloroform as developing solvent. After removal of the first fraction containing the unreacted starting material, the chloroform eluate containing the object compound is concentrated under reduced pressure, and the residue is treated with toluene to give white crystalline 5 - o - chlorophenyl - 7 - ethyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin - 2 - one melting at 204–206° C. (from a mixture of toluene and ethanol).

EXAMPLE 5

5 - p - chlorophenyl - 6,7 - dimethyl-1,2-dihydro-3H-thieno - [2,3-e][1,4]diazepin - 2 - one (3.0 g.) is suspended in 70 ml. of toluene. The suspension is heated to 40° C. whereupon 0.58 g. of sodium methoxide is added, and the mixture is refluxed to make a homogeneous pale brown solution. After about 10 ml. of the methanol and toluene are distilled off, 1.3 g. of dimethyl sulfate is added slowly, and the resulting mixture is refluxed for 1 hour. After cooling, the toluene layer is washed with water, then with a sodium hydrogen carbonate solution, dried over sodium sulfate, and the toluene is distilled off. To the oily residue are added hexane and a small amount of ethanol. Crystallization takes place when the flask is scratched. The crystals are collected by suction filtration and recrystallized from a mixture of hexane and ethanol to give white crystalline 5 - p - chlorophenyl - 1,6,7-trimethyl - 1,2 - dihydro - 3H - thieno - [2,3-e][1,4]diazepin-2-one, melting at 182–184° C., in 76% yield.

Using the procedures set forth in the above examples, but substituting equivalent amounts of the appropriate starting materials, the following compounds are also produced:

(1) 5 - p - chlorophenyl - 6,7-dimethyl-1,2-dihydro-3H-thieno - [2,3-e][1,4]diazepin - 2 - one, melting at 243–245° C., and its hydrobromide, melting at 262–263° C.

(2) 5 - m - trifluoromethylphenyl - 6,7,dimethyl-1,2-dihydro - 3H - thieno - [2,3-e][1,4]diazepin-2-one, melting at 220°–222° C.

(3) 5 - o - chlorophenyl - 7 - isopropyl-1,2-dihydro-3H-thieno-[2,3-e][1,4]diazepin - 2 - one, melting at 243–246° C.

(4) 5 - o - chlorophenyl - 7 - methyl-1,2-dihydro-3H-thieno - [2,3-e][1,4]diazepin-2-one, melting at 212–213° C.

(5) 5 - o - chlorophenyl - 7 - ethyl-1-methyl-1,2-dihydro-3H - thieno - [2,3-e][1,4]diazepin-2-one, melting at 105–106° C.

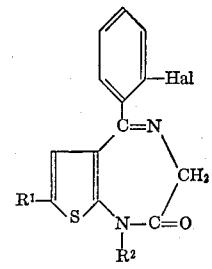
(6) 5 - phenyl - 1,2,7,8,9,10 - hexahydro - 3H,6H - [1]cycloheptathieno - [2,3-e][1,4]diazepin-2-one, melting at 228–229° C.

(7) 5 - phenyl - 1 - methyl - 1,2,7,8,9,10 - hexahydro-3H,6H - [1]cycloheptathieno - [2,3-e][1,4]diazepin-2-one, melting at 150–151° C.

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

What is claimed is:

1. Thieno-[2,3-e][1,4]diazepin-2-ones of the formula:



wherein R^1 is a lower alkyl group of from 1 to 2 carbon atoms; R^2 is a member selected from the group consisting of a hydrogen atom and a methyl group; and Hal represents a halogen atom; and the pharmaceutically acceptable acid addition salts thereof.

2. The compound of Claim 1: 5 - o - chlorophenyl-7-ethyl - 1,2 - dihydro - 3H - thieno - [2,3-e][1,4]diazepin-2-one.

3. The compound of Claim 1: 5 - o - chlorophenyl-7-ethyl - 1 - methyl - 1,2 - dihydro - 3H-thieno-[2,3-e]-[1,4]diazepin-2-one.

4. Th compound of Claim 1: 5 - o - chlorophenyl-7-methyl - 1,2 - dihydro - 3H - thieno - [2,3-e][1,4]diazepin-2-one.

5. The compound of Claim 1: 5 - o - chlorophenyl-1,7 - dimethyl - 1,2 - dihydro - 3H - thieno - [2,3-e][1,4] diazepin-2-one.

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HENRY R. JILES, Primary Examiner

R. T. BOND, Assistant Examiner

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