

PATENT SPECIFICATION

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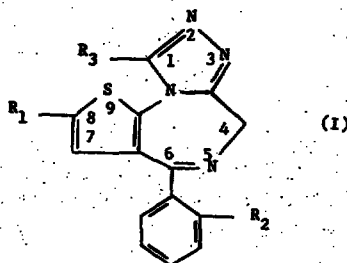
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(54) SUBSTITUTED 6-ARYL-4H-s-TRIAZOLO-[3,4c]-
 THIENO-[2,3e]-1,4-DIAZEPINES AND ACID ADDITION
 SALTS THEREOF

(71) We, BOEHRINGER INGELHEIM GMBH, a German Body Corporate of Ingelheim am Rhein, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel substituted 6-aryl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepines, the acid addition salts thereof and to processes for their preparation. The novel compounds possess interesting physiological activity.

According to one feature of the present invention there are provided compounds of the general formula:—



(wherein

R₁ represents a bromine atom;

R₂ represents a hydrogen, fluorine, chlorine or bromine atom; and

R₃ represents a hydrogen atom or an alkyl or hydroxyalkyl group with 1 to 4 carbon atoms) and the acid addition salts thereof.

The acid addition salts useful for incorporation in pharmaceutical compositions are physiologically compatible acid addition salts thereof. Other acid addition salts may however be useful in the preparation of compounds of formula I and physiologically compatible acid addition salts thereof.

The compounds of general formula I and the physiologically compatible acid addition salts thereof of the present invention possess interesting physiological activities. In the course of various pharmacological tests we have found that compounds of the present invention possess anxiolytic, tensiolytic and muscle-relaxing properties and in particular an anticonvulsive activity. The compounds of the present invention, in general, appear to increase the intake of food in the case of warm-blooded animals. The compounds of formula I and their physiologically compatible acid addition salts thereof also possess low toxicity. Compounds of the present invention which have been tested have been found to be superior to the thieno-1,4-diazepines without the additional triazole ring, as described, for example, in German Offenlegungsschrift 2,155,403 and 2,221,623. In particular the anticonvulsive activity of the tested compounds, determined by the so-called

pentetrazole test, indicated an anticonvulsive activity comparable to the known 8-alkyl-6-aryl-thieno-[2,3e]-4H-s-triazolo-[3,4c]-1,4-diazepines described in German Offenlegungsschrift 2,229,845. The tested compounds, however, were found to possess an anticonvulsive activity an order of magnitude greater than the tested prior art compounds.

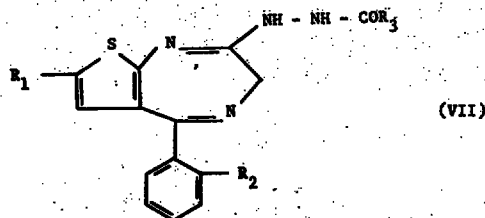
British Patent Specification No. 1,456,161 claims certain novel substituted 6-aryl-4H-s-triazolo-[4,5c]-thieno-[2,3e]-1,4-diazepines. The compounds of the present invention fall within the ambit of claims of British Patent Specification No. 1,456,161, but there is no specific reference to the said British Patent Specification to any compound of the present invention. The present invention is based upon the discovery that the 8-bromo-6-aryl-4H-s-triazolo-[4,5c]-thieno-[2,3e]-1,4-diazepines described and claimed herein exhibit a substantially superior anticonvulsive activity and possess a substantially superior therapeutic index ($LD_{50}:ED_{50}$) to the corresponding 8-chloro compounds.

Preferred compounds according to the present invention, by virtue of their favourable physiological activity, include compounds of formula I (as hereinbefore described) wherein R_2 represents a chlorine or bromine atom as well as compounds of formula I wherein R_3 represents a methyl group e.g. 8-bromo-6-*o*-bromophenyl-1-methyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine.

Especially preferred compounds according to the present invention, by virtue of their especially favourable physiological activity, include the following compounds:— 8-bromo-6-*o*-chlorophenyl-1-methyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = Br$, $R_2 = Cl$, $R_3 = CH_3$), 8-bromo-6-*o*-chlorophenyl-1-(2-hydroxyethyl)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = Br$, $R_2 = Cl$, $R_3 = CH_2CH_2OH$) and acid addition salts thereof.

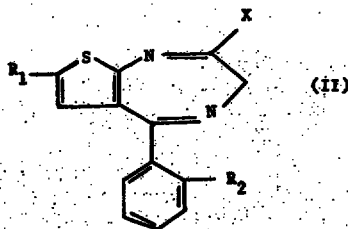
The compounds of formula I according to the present invention may, for example, be prepared by the following processes (a) to (d), which processes constitute a further feature of the present invention:—

a) the cyclization of the compound of the formula:

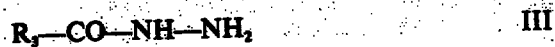


(wherein R_1 , R_2 and R_3 are as hereinbefore defined) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined) is obtained.

The compounds of formula VII are preferably first prepared by reacting a compound of the formula:—

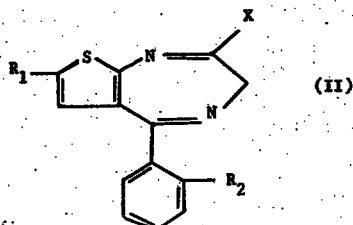


(wherein R_1 and R_2 are as hereinbefore defined and X represents an atom or group removable as an anion) with a compound of the formula:—



(wherein R_3 is as hereinbefore defined) whereby a compound of formula VII (as hereinbefore defined) is obtained.

b) the reaction of a compound of the formula:—



(wherein R_1 and R_2 are as hereinbefore defined and X represents an atom or group removable as an anion) with a compound of the formula:—

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III

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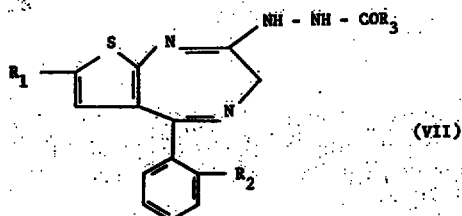
(wherein R_3 is as hereinbefore defined) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are hereinbefore defined) is obtained.

A compound of formula II is preferably used in which X represents a halogen atom or a SH— or NH₂— group or an alkoxy or alkylmercapto group with 1—3 carbon atoms.

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The cyclization and/or the reaction of the compounds of formula II and III is advantageously effected at a temperature of from 100 to 250°C either without a solvent or in the presence of a solvent, such as methanol, ethanol, dioxan, chloroform, tetrahydrofuran, benzene, toluene, xylene or mixtures of these solvents and preferably in the presence of an acid catalyst (for example hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, acetic acid, propionic acid, benzene-sulfonic acid or toluenesulfonic acids). The cyclization and/or the reaction of the compounds of formulae II and III is generally allowed to proceed to yield the final product without isolation of the intermediate product of formula:—

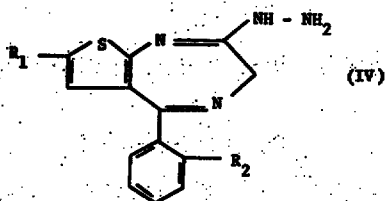
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(wherein R_1 , R_2 and R_3 are as hereinbefore defined). When however, the cyclization and/or the reaction is effected under milder reaction conditions (e.g. at room temperature) it is possible to isolate the intermediate products without difficulty.

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c) the reaction of a compound of the formula:—



(wherein R_1 and R_2 are as hereinbefore defined) with a compound of the formula:—

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V

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(wherein R_3 is as hereinbefore defined) or a reactive derivative thereof, whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined) is obtained.

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The functional derivative of the acid of general formula V is, for example, an orthoester of general formula $R_3\text{—C(OR')}_3$ (Va) an iminoether of general formula

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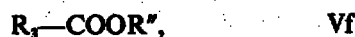
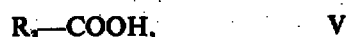
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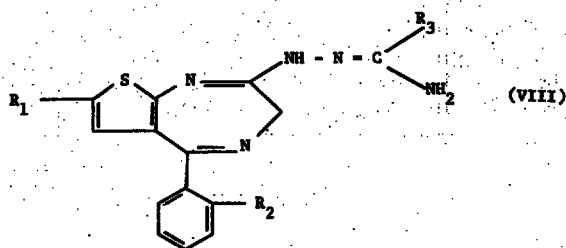
$R_3-C(=NH)-OR'$ (Vb), an amidine of general formula $R_3-C(=NH)-NH_2$ (Vc), an amide of general formula R_3-CONH_2 (Vd), a thioamide of general formula R_3-CSNH_2 (Ve), an ester of general formula R_3-COOR'' (Vf), an acid anhydride of general formula $(R_3-CO)_2O$ (Vg), an acid halide of general formula $R_3-COHal$ (Vh) or a nitrile of general formula R_3-CN (Vi) (in which R_3 is as hereinbefore defined, R' represents an alkyl group with 1-3 carbon atoms and R'' represents an aliphatic, araliphatic or aryl group e.g. a methyl, ethyl or nitrophenyl group).

The compounds of formula VII as hereinbefore defined are also preferably first prepared by reacting a compound of formula IV (as hereinbefore defined) with a compound of the formula:—



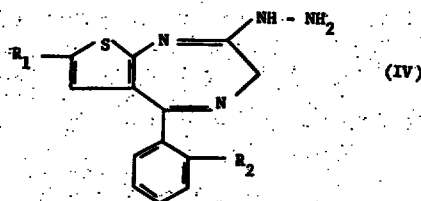
(wherein R_3 and R'' are as hereinbefore defined) whereby a compound of formula VII (as hereinbefore defined) is obtained. Where a compound of formula (Vh) is used Hal preferably represents a chlorine atom.

d) the cyclization of a compound of the formula:—

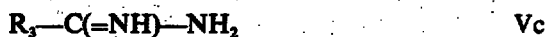


(wherein R_1 , R_2 and R_3 are as hereinbefore defined) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined) is obtained.

The compounds of formula VIII are preferably first prepared by reacting a compound of the formula:—



(wherein R_1 and R_2 are as hereinbefore defined) with a compound of the formula:—



(wherein R_3 is as hereinbefore defined) whereby a compound of formula VIII (as hereinbefore defined) is obtained.

The iminoethers of formula Vb and the amidines of formula Vc are conveniently used in the form of their salts with mineral acids e.g. in the form of their hydrochloride.

The reaction conditions for the cyclization and/or the reaction of the compound of formula IV with the compound of formula V or a reactive derivative thereof are preferably chosen according to the acid derivative used. The cyclization and/or the reaction may be effected without solvent or in the presence of a solvent (e.g. in methanol, ethanol, chloroform, tetrahydrofuran, benzene, toluene or in a mixture of these solvents) and without a catalyst or in the presence of an acid catalyst (e.g. hydrochloric acid, sulfuric acid, phosphoric acid,

polyphosphoric acid, acetic acid, propionic acid, benzenesulfonic acid or toluenesulfonic acids). The presence of a base, such as for example 2-methylimidazole, as a catalyst is also useful. The cyclization and/or the reaction is conveniently effected at a temperature of from 0°C to 300°C, preferably 20 to 180°C.

The following methods are special variants of this process:

Method I

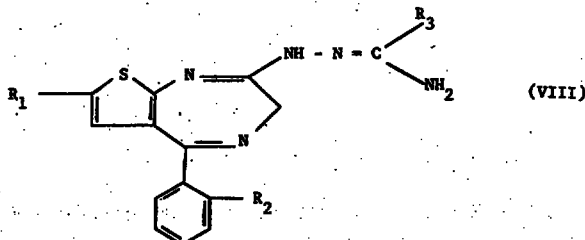
In this case the acid derivative of formula V is the orthoester $R_3-C(OR')_3$ (wherein R_3 and R' are as hereinbefore defined). Usually, the reaction is effected in the presence of an excess of the orthoester, serving simultaneously as solvent, at a temperature of from 90 to 100°C or alternatively in the presence of a solvent mentioned before, optionally in the presence of a previously mentioned catalyst, and at a temperature of from room temperature to the reflux temperature of the reaction mixture.

Method II

In this case the acid derivative of general formula V is an iminoether of general formula $R_3-C(=NH)-OR'$ (wherein R_3 and R' are as hereinbefore defined). It is convenient to effect the reaction in the presence of one of the previously mentioned solvents and at a temperature between room temperature and the reflux temperature of the reaction mixture.

Method III

In this case the acid derivative of general formula V is an amidine of general formula $R_3-C(=NH)-NH_2$. It is convenient to effect the reaction in the presence of a basic catalyst, such as 2-methylimidazole at an elevated temperature, e.g. from 150 to 250°C. When a lower reaction temperature is employed e.g. 0 to 150°C, conveniently at room temperature, an intermediate product is first formed having the following formula:—



(wherein R_1 , R_2 , and R_3 are as hereinbefore defined). This intermediate product may, if desired be isolated and subsequently subjected to cyclization by heating same to 150 to 250°C. However, isolation of this intermediate is not necessary and cyclization of the intermediate may be effected *in situ*.

Method IV

In this case the acid derivative of general formula V is an amide or thioamide of formula R_3-CONH_2 or R_3-CSNH_2 (wherein R_3 is as hereinbefore defined). The reaction may be effected with or without a solvent and either with or without a catalyst at for example a temperature between 0° and 300°C.

Method V

In this case the acid derivative of general formula V is an ester of formula R_3-COOR'' , an anhydride of general formula $(R_3CO)_2O$, an acid halide of general formula $R_3-COHal$ or a nitrile of general formula R_3-CN (wherein R_3 and R'' are as hereinbefore defined). The intermediate product of general formula VII is formed first, and may be cyclized as indicated for process (a).

The final products of general formula I may be converted, if desired, into their acid addition e.g. their physiologically compatible acid addition salts, in the conventional way. Acids suitable for salt formation include for example, hydrohalic acids, sulfuric acid, phosphoric acid, nitric acid, cyclohexylsulfaminic acid, citric acid, tartaric acid, ascorbic acid, maleic acid, formic acid, salicylic acid, methane sulfonic acid or toluenesulfonic acids.

The starting compounds of general formula III and V are known from the literature. While production of the compounds of general formulae VII and VIII.

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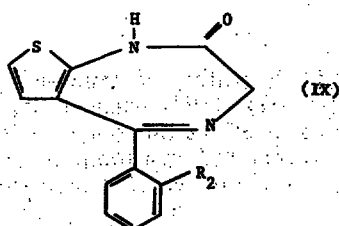
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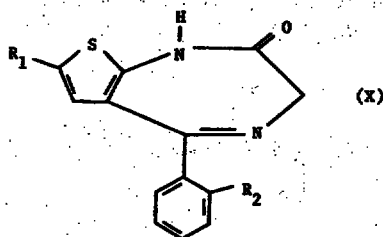
has already been described, production of the compounds of general formulae II and IV is described in the following:

The hydrazine derivatives of general formula IV may, for example, be produced by reacting compounds of general formula II with hydrazine. This may, if desired, be effected in one of the above-mentioned solvents, one of the previously mentioned acid catalysts being present, if desired. The temperature of the reaction is conveniently between room temperature and the reflux temperature of the reaction mixture.

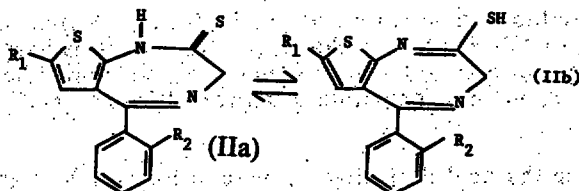
The compounds of general formula II may, for example, be reacted either directly with compounds of general formula III to yield the final compounds of general formula I or alternatively may, for example, be reacted with hydrazine to yield compounds of general formula IV. The compounds of formula II are conveniently produced by brominating a compound of formula IX (which compounds are known from the literature)



(wherein R₂ is as hereinbefore defined) with bromine or N-bromo-succinimide in the conventional manner followed by reaction of the compounds obtained, of general formula:—

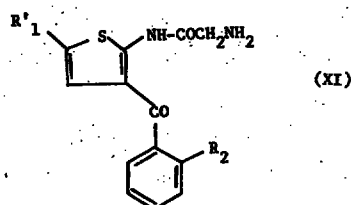


(wherein R₁ and R₂ are as hereinbefore defined) (certain of which compounds are known) with phosphorus pentasulfide, in the presence of a solvent such as pyridine, dimethylformamide or tetrahydrofuran or a mixture thereof. The reaction may be effected at a temperature of from room temperature to the reflux temperature of the reaction mixture. Compounds of general formula II in which X represents an —SH group are thus obtained. The mercapto compounds are in tautomeric equilibrium with the corresponding thio compounds as shown in the following formula-scheme:



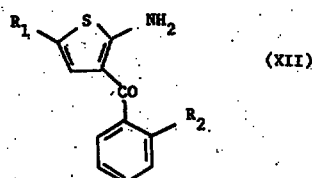
(wherein R₁ represents a bromine atom and R₂ is as hereinbefore defined). These compounds may be reacted with, for example, sodium methoxide or sodium amide in a solvent to yield the corresponding salt which may then be reacted without previous isolation with alkylating agents such as methyl or another alkyl iodide to yield compounds of general formula II, wherein X represents a thialkyl group with 1 to 4 carbon atoms.

The compounds of general formulae IX and X may also be obtained by intramolecular cyclization of compounds of general formula:—

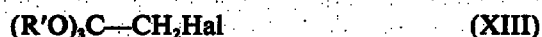


wherein R_2 is as hereinbefore defined and R'_1 represents a hydrogen or bromine atom. An especially advantageous variant of this reaction consists of effecting the cyclization by boiling in toluene on a water-separator using silica gel as the dehydrating agent. When the reaction is effected according to the above-mentioned preferred variant higher yields and purer products are, in general, obtained.

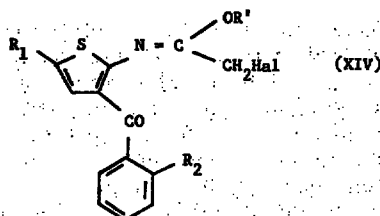
Compounds of general formula II, in which X represents an alkoxy group, may be obtained, for example, by reacting known aminoketones of general formula



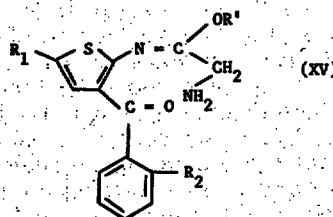
(wherein R_1 and R_2 are as hereinbefore defined) with a halogen-ortho-acetate of general formula



(wherein R' represents an alkyl group with 1 or 2 carbon atoms and Hal represents chlorine, bromine or iodine) to yield a compound of general formula

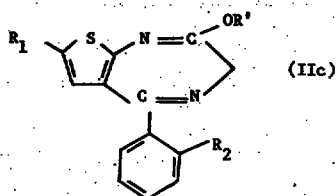


wherein R' , R_1 , R_2 and Hal are as hereinbefore defined. In a case where Hal represents a chlorine atom, it is useful to first exchange the aliphatically bound chlorine atom in the compound of general formula XIV by iodine, by means of a Finkelstein-reaction (e.g. by reacting with NaI in acetone). Then, the halogen compound obtained is, for example, reacted with ammonia in dioxan or tetrahydrofuran. An amino compound of the formula:



(wherein R' , R_1 and R_2 are as hereinbefore defined) is thus obtained as an intermediate, which, however, converts directly to a compound of the formula:

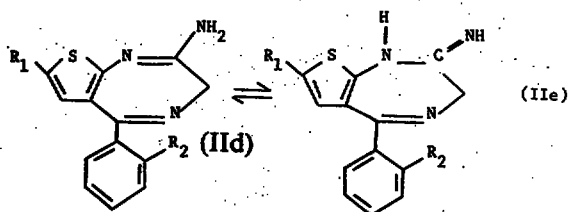
18



(wherein R' , R_1 and R_2 are as hereinbefore defined).

Compounds of general formula II, in which X represents an amino group, may, for example, be produced by reacting ammonia with compounds of general formula X, which were obtained by bromination of compounds of general formula IX. It is useful to effect the reaction in the presence of a solvent such as tetrahydrofuran and also in the presence of a Lewis acid such as, for example, titanium chloride.

The amino compound is in tautomeric equilibrium with the imino compound as shown in the following formula-scheme:



where R_1 and R_2 have the above-mentioned meanings.

According to a yet still further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula I as hereinbefore defined or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient. The compositions according to the invention may also include, if desired, other physiologically active compounds, for example spasmolytics or β -receptor blockers.

The compositions according to the invention may be presented, for example, in a form suitable for oral, parenteral or rectal administration.

The compounds according to the invention may be presented in the conventional pharmacological forms of administration, such as tablets, coated tablets, solutions, emulsions, powders, capsules or sustained release forms. Conventional pharmaceutical excipients as well as the usual methods of production may be employed for the preparation of these forms. Tablets may be produced, for example, by mixing the active ingredient or ingredients with known excipients, such as for example with diluents, such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talcum, and/or agents for obtaining sustained release, such as carboxypolymethylene, carboxymethyl cellulose, cellulose acetate phthalate, or polyvinylacetate.

The tablets may if desired consist of several layers. Coated tablets may be produced by coating cores, obtained in a similar manner to the tablets, with agents commonly used for tablet coatings for example polyvinyl pyrrolidone or shellac, gum arabic, talcum, titanium dioxide or sugar. In order to obtain sustained release or to avoid incompatibilities, the core may consist of several layers too. The table-coat may also consist of several layers in order to obtain sustained release, in which case the excipients mentioned above for tablets may be used.

Syrups of the active ingredient according to the invention or combinations of active ingredients may additionally contain a sweetener, such as saccharin, glycerin or sugar, and/or taste improving agents such as flavourings e.g. vanillin or orange extract. They may also contain suspension agents or thickeners, such as sodium carboxymethyl cellulose, wetting agents such as for example condensation products of fatty alcohols with ethylene oxide, or preservatives, such as *p*-hydroxybenzoates.

Injection solutions may, for example, be produced in the conventional manner, such as by the addition of preservation agents, such as *p*-hydroxybenzoates, or stabilizers, such as Complexons. The solutions are then filled into injection vials or ampoules.

Capsules containing one or several active ingredients may be produced for example by mixing the active ingredients with inert carriers, such as lactose or sorbitol, and filling the mixture into gelatin capsules.

Suitable suppositories may, for example be produced by mixing the active ingredient or active ingredient combinations with the conventional carriers envisaged for this purpose, such as neutral fats or polyethyleneglycol or derivatives thereof.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms. Each dosage unit preferably contains 0.05 to 50 mg. of the said active ingredient and especially 0.1 to 25 mg. (orally) of the said active ingredient. The daily dosage is preferably from 5 to 150 mg. of the said active ingredient.

The following examples illustrate the preparation of compounds according to the invention, and also pharmaceutical compositions containing such compounds as active ingredients:—

Preparation of Starting Materials

The starting compounds of formula X are obtained as follows:

a) In a similar manner to the example, described in German Offenlegungsschrift No. 2,221,623, 0.03 mol of a compound of formula IX are dissolved or suspended in 60 cc of chloroform and mixed with 4.7 g of bromine over a period of 5 minutes after the addition of 6 cc of pyridine. Stirring is continued for 45 minutes at 25° to 30°C, whereby the compound of general formula X separates out in the form of a yellow precipitate, which is filtered off with suction and washed with ether.

10 to 12 g of the compound according to general formula X are obtained.

The product of this process may be used for thionization in its crude form without purification.

b) 17 g of 2-bromoacetyl-amino-3-[aroyl]-thiophene are dissolved in 200 to 250 cc of chloroform and mixed at room temperature with 20 cc of pyridine, followed by 5 cc of bromine. After 2-hours stirring, the reaction mixture is shaken several times with water, the chloroform phase is dried with $MgSO_4$, evaporated and the residue stirred with isopropyl ether.

Yield: 10 to 15 g of 2-bromoacetyl-amino-3-[aroyl]-5-bromothiophene.

10 g of this latter compound are dissolved in 400 cc of ethyl acetate and gaseous ammonia is introduced into the reaction mixture at room temperature over the course of two hours. The precipitated ammonium chloride is filtered off with suction, the filtrate is evaporated *in vacuo* and 7 to 8 g of the aminoacetyl-amino compound of formula XI are obtained.

7 g of this compound are boiled in 80 cc of toluene with 25 g of silica gel in a water-separator for 1 hour. The mixture is cooled to 50 to 60°C and 50 cc of methanol are added. After suction filtration and washing, 3 to 4 g of the desired compound of formula X are obtained from the filtrate.

The starting compounds of general formula II are obtained as follows:

0.2 mol of 2-amino-5-bromo-3-(orthochlorobenzoyl)-thiophene of formula XII is boiled while stirring with 78.4 g (0.4 mol) of ethyl chloroorthoacetate (see formula XIII) in one ltr. of benzene for 8 hours, 0.01 ml of trifluoroacetic acid being added to the reaction mixture after approximately 4 hours. The solvent is evaporated off and the remaining orthoester is removed under high vacuum.

The crude material is stirred in 1.5 ltrs. of acetone with 16 to 20 g of sodium iodide for 6 hours at room temperature. The reaction mixture is evaporated and the residue taken up in methylene chloride. The methylene chloride solution is shaken several times with iced water and dried over magnesium sulfate.

The residue (crude product of formula XIV) is taken up in 150 cc of absolute dioxan and ammonia gas is introduced into the reaction mixture over the course of 1 to 2 hours at room temperature. The solvent is then removed *in vacuo*, the residue taken up in methylene chloride, washed with iced water, the solution dried over magnesium sulfate and evaporated. The compound of formula IIc remains in the form of an oil and may be reacted as described above to yield the hydrazino derivative in a similar manner to the thio compound.

23

I. Production Examples.

Example 1.

8-Bromo-6-*o*-chlorophenyl-1-methyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine

a) 11.5 g of 7-bromo-5-*o*-chlorophenyl-3H-[2,3e]-thieno-1,4-diazepin-2-one (see German Offenlegungsschrift No. 22 21 623) of formula X are heated to 55—60°C with 100 cc of absolute pyridine and 6.5 g of phosphorus pentasulfide for 4 hours while stirring. The reaction mixture is allowed to cool and is then poured into 100 cc of saturated ice-cold sodium chloride solution. The precipitate is filtered off with suction, washed with water, and subsequently dissolved in 100 cc of methylene chloride. The solution is dried, evaporated and the residue treated with a little methylene chloride. After filtration with suction, 6 g of brown crystals of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione of formula II are obtained, m.p. 214°C, decomp.

b) 6.0 g of the product of (a) are suspended in 100 cc of tetrahydrofuran and stirred at room temperature with 1.2 g of hydrazine hydrate for 20 minutes. After evaporation of the reaction mixture to approximately 10 cc, 20 cc of ether are added and the crystals are filtered off with suction. Yield: 5.2 g of 7-bromo-5-(*o*-chlorophenyl)-2-hydrazino-3H-[2,3e]-thieno-1,4-diazepin (m.p. 300°C decomp.) of formula IV.

c) 5.2 g of the product of (b) are suspended in 50 cc of orthiotriethyl acetate and heated to 80°C. After approximately 30 minutes a clear solution is first obtained, from which colourless crystals later separate out. The reaction mixture is allowed to cool, the crystals are filtered off with suction and washed with ether. Yield: 5 g of the title compound, m.p. 211—213°C.

Example 2.

8-Bromo-6-[*o*-chlorophenyl]-1-hydroxymethyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine

4.8 g of 7-bromo-5-[*o*-chlorophenyl]-3H-[2,3e]-thieno-1,4-diazepine-2-thione (see Example 1a) are heated together with 3.4 g of glycolic acid hydrazide in 100 cc of *n*-butanol in an atmosphere of nitrogen, until the mixture is boiling. Boiling is continued under reflux for 5 hours, the mixture is partially evaporated and the title compound is crystallized out by the addition of isopropyl ether.

The title compound of m.p. 224—226°C is obtained in a yield of 60% of theory.

The following final products were obtained according to the methods described above:—

Example No.	R ₁	R ₂	R ₃	m.p. °C	m.p. °C of Hydrazide
3	Br	Br	CH ₃	205—206	—
4	Br	F	CH ₃	210	—
5	Br	H	CH ₃	284	—
6	Br	Cl	H	216—218	—
7	Br	Cl	iC ₃ H ₇	203—205	—

Pharmaceutical Composition Examples

Example A.

Coated Tablets

1 coated tablet consists of:

5	active ingredient of formula I according to the invention	1.0 mg	5
	lactose	28.5 mg	
	corn starch	19.0 mg	
	gelatin	1.0 mg	
10	magnesium stearate	0.5 mg	10
		<u>50.0 mg</u>	

Production:

15 A mixture of the active ingredient with lactose and corn starch is granulated
with a 10% aqueous gelatin solution through a screen of 1 mm mesh-size, dried at
40°C and tritured once more through a screen. The granulate thus obtained is
mixed with magnesium stearate and pressed into tablet cores. The cores obtained
are covered with a coating in the usual way, the coating being applied with the aid
of an aqueous suspension of sugar, titanium dioxide, talcum and gum arabic. The
finished coated tablets are polished with beeswax. Final weight of coated table:
20 100 mg. 20

Example B.

Tablets

25	Active ingredient of formula I according to the invention	0.5 mg	25
	lactose	50.0 mg	
	corn starch	43.5 mg	
	soluble starch	5.0 mg	
	magnesium stearate	1.0 mg	
		<u>100.0 mg</u>	

30 Production:
The active ingredient and magnesium stearate are granulated in an aqueous
solution of the soluble starch, the granulate is dried and mixed well with lactose
and corn starch. The mixture is then pressed into tablets each weighing 100 mg and
each containing 0.5 mg of active ingredient. 30

35 Example C. 35

Suppositories

1 suppository consists of:

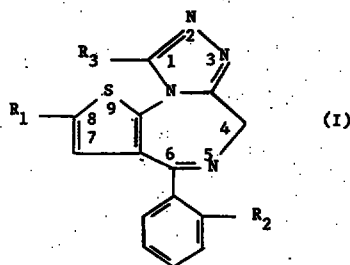
40	active ingredient of formula I according to the invention	5.0 mg	40
	suppository mass	1,695.0 mg	

Production:

The finely pulverized substance is stirred into the molten suppository mass with the aid of an immersion homogenizer, the mass being cooled to 40°C. At 35°C the mass is poured into slightly precooled moulds.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:



(wherein

R_1 represents a bromine atom;

R_2 represents a hydrogen, fluorine, chlorine or bromine atom and

R_3 represents a hydrogen atom or an alkyl or hydroxyalkyl group with 1 to 4 carbon atoms) and the acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R_2 represents a chlorine or bromine atom.

3. 8-Bromo-6-(*o*-chlorophenyl)-1-methyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine and acid addition salts thereof.

4. 8-Bromo-6-(*o*-bromophenyl)-1-methyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine and acid addition salts thereof.

5. 8-Bromo-6-(*o*-chlorophenyl)-1-hydroxymethyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine and acid addition salts thereof.

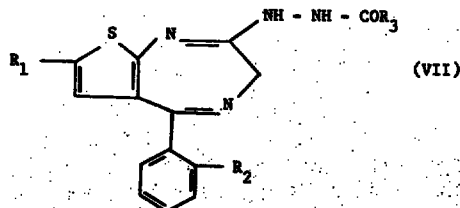
6. Compounds of formula I as defined in claim 1 (wherein R_1 represents a bromine atom; R_2 represents a fluorine, chlorine or bromine atom; and R_3 represents a hydrogen atom or an alkyl or hydroxyalkyl group with 1 to 2 carbon atoms) and the acid addition salts thereof.

7. Compounds as claimed in claim 1 in the form of physiologically compatible acid addition salts.

8. Compounds as claimed in claim 6 in the form of physiologically compatible acid addition salts thereof.

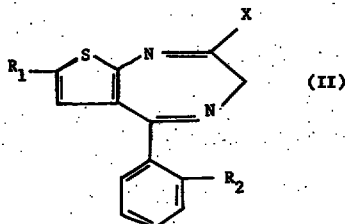
9. Compounds as claimed in claim 6 other than as claimed in any of claims 3 to 5, as herein specifically disclosed.

10. A process for the preparation of compounds of formula I as defined in claim 1 which comprises cyclizing a compound of the formula:



(wherein R_1 , R_2 and R_3 are as defined in claim 1 whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1) is obtained.

11. A process as claimed in claim 10 wherein the compound of formula VII is first prepared by reacting a compound of the formula:—

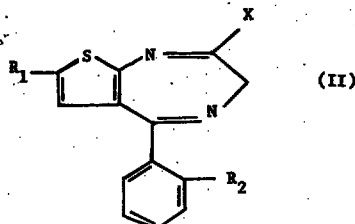


(wherein R_1 and R_2 as defined in claim 1 and X represents an atom or group removable as an anion) with a compound of the formula:—



(wherein R_3 is as defined in claim 1) whereby a compound of formula VII (as defined in claim 10) is obtained.

12. A process for the preparation of compounds of formula I as defined in claim 1 which comprises reacting a compound of the formula:—



(wherein R_1 and R_2 are as defined in claim 1 and X represents an atom or group removable as an anion) with a compound of the formula:—



(wherein R_3 is as defined in claim 1) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1) is obtained.

13. A process as claimed in claim 12 wherein a compound of formula II is used wherein R represents a halogen atom or a SH— or NH_2 group or an alkoxy or alkylmercapto group with 1 to 3 carbon atoms.

14. A process as claimed in any of claims 10 to 13 wherein the cyclization and/or the reaction of the compounds of formulae II and III is effected at a temperature of from 100 to 250°C.

15. A process as claimed in any of claims 10 to 14 wherein the cyclization and/or the reaction of the compounds of formulae II and III is effected in the presence of an acid catalyst.

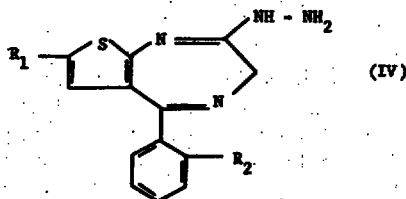
16. A process as claimed in claim 15 wherein the acid catalyst comprises hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, acetic acid propionic acid, benzenesulfonic acid or toluenesulfonic acids.

17. A process as claimed in any of claims 10 to 16 wherein the cyclization and/or the reaction of the compounds of formulae II and III is effected in the presence of methanol, ethanol, dioxan, chloroform, tetrahydrofuran, benzene, toluene or xylene or a mixture thereof as solvent.

18. A process as claimed in claim 10 and any of claims 14 to 17 for the preparation of compounds of formula I (as defined in claim 6) wherein a compound of formula VI (wherein R_1 , R_2 and R_3 are as defined in claim 6) is cyclized.

19. A process as claimed in claim 12 to 17 for the preparation of compounds of formula I (as defined in claim 6) wherein a compound of formula II (wherein R_1 and R_2 are as defined in claim 6) is reacted with a compound of formula III (wherein R_3 is as defined in claim 6).

20. A process for the preparation of compounds of formula I as defined in claim 1 which comprises reacting a compound of the formula:—

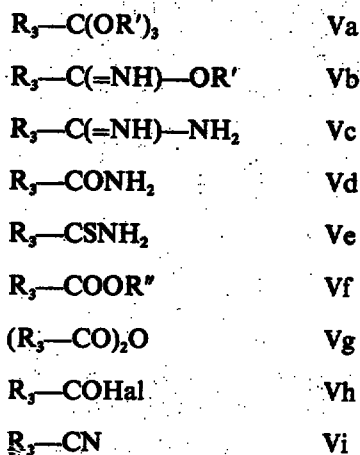


(wherein R_1 and R_2 are as defined in claim 1) with a compound of the formula:—



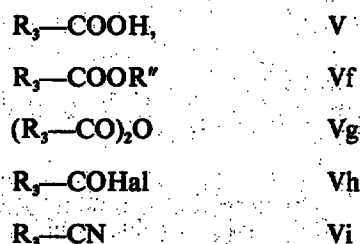
(wherein R_3 is as defined in claim 1) of a reactive derivative thereof, whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1) is obtained.

21. A process as claimed in claim 20 wherein the reactive derivative of the compound of formula V is a compound of the formula:—



(wherein R_3 is as defined in claim 20, R' represents an alkyl group with 1—3 carbon atoms and R'' represents an aliphatic, araliphatic or aryl group).

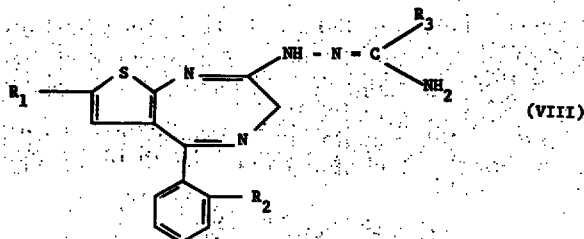
22. A process as claimed in claim 10 wherein the compound of formula VII is first prepared by reacting a compound of formula IV (as defined in claim 20) with a compound of the formula:—



(wherein R_3 is as defined in claim 20 and R' and R'' are as defined in claim 21) whereby a compound of formula VII (as defined in claim 10) is obtained.

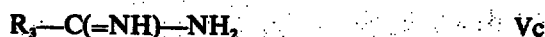
23. A process as claimed in claim 21 or claim 22 wherein a compound of formula Vh is used in which Hal represents a chlorine atom.

24. A process for the preparation of compounds of formula I as defined in claim 1 which comprises cyclizing a compound of the formula:—



(wherein R_1 , R_2 and R_3 are as defined in claim 1) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1) is obtained.

25. A process as claimed in claim 24 wherein the compound of formula VIII is first prepared by reacting a compound of formula IV as defined in claim 20 with a compound of the formula:—



(wherein R_3 is as defined in claim 1) whereby a compound of formula VIII (as defined in claim 24) is obtained.



26. A process as claimed in claim 21 or claim 25 wherein the compound of formula Vb or Vc is used in the form of its salt with a mineral acid.

27. A process as claimed in claim 26 wherein the compound of formula Vb and Vc are used in the form of the hydrochloride salt.

28. A process as claimed in claim 21 wherein a compound of formula Vf is used in which R' represents a methyl, ethyl or nitrophenyl group.

29. A process as claimed in any of claims 20 to 28 wherein the cyclization and/or the reaction of the compound of formula IV with the compound of formula V or a reactive derivative thereof is effected in the presence of methanol, ethanol, chloroform, tetrahydrofuran, benzene or toluene or a mixture thereof as solvent.

30. A process as claimed in any of claims 20 to 29 wherein the cyclization and/or the reaction of the compound of formula IV with the compound of formula V or a reactive derivative thereof is effected in the presence of an acid catalyst.

31. A process as claimed in claim 30 wherein the acid catalyst comprises hydrochloric acid, sulphuric acid, phosphoric acid, polyphosphoric acid, acetic acid, propionic acid, benzenesulphonic acid or toluenesulphonic acid.

32. A process as claimed in any of claims 20 to 29 wherein the cyclization and/or the reaction of the compound of formula IV with the compound of formula V or a reactive derivative thereof is effected in the presence of a base.

33. A process as claimed in claim 32 wherein the base comprises 2-methylimidazole.

34. A process as claimed in any of claims 20 to 33 wherein the cyclization and/or the reaction of the compound of formula IV with the compound of formula V or a reactive derivative thereof is effected at a temperature of from 0 to 300°C.

35. A process as claimed in claim 34 wherein the cyclization and/or the reaction of the compound of formula IV with the compound of formula V or a reactive derivative thereof is effected at a temperature of from 20 to 180°C.

36. A process as claimed in claim 21 and claims 30 to 35 wherein the compound of formula IV (as defined in claim 20) is reacted with a molar excess of a compound of formula Va at a temperature of from 90 to 100°C.

37. A process as claimed in claim 21 or 25 wherein the compound of formula IV (as defined in claim 20) is reacted with a compound of formula Vc (as defined in claim 21) at a temperature of from 150 to 250°C and optionally in the presence of a basic catalyst.

38. A process as claimed in claim 23 wherein the reaction between the compound of formula IV (as defined in claim 20) and the compound of formula Vc (as defined in claim 21) is effected at a temperature of from 0 to 150°C whereby the compound of formula VIII thus formed is isolated from the reaction mixture.

39. A process as claimed in any of claims 20, 21 and 24 to 36 for the preparation of compounds of formula I (as defined in claim 6) wherein a compound of formula IV (wherein R₁ and R₂ are as defined in claim 6) is reacted with a compound of formula V (wherein R₃ is as defined in claim 6) or a reactive derivative thereof.

40. A process as claimed in any of claims 24 to 38 for the preparation of compounds of formula I (as defined in claim 6) wherein a compound of formula VIII (wherein R₁, R₂ and R₃ are as defined in claim 6) is cyclized.

41. A process as claimed in any one of claims 10 to 17 and 20 to 38 wherein the compound of formula I thus obtained is converted into an acid addition salt thereof.

42. A process as claimed in any of claims 18, 19, 39 and 40 wherein the compound of formula I thus obtained is converted into an acid addition salt thereof.

43. A process as claimed in any one of claims 10 to 17, 20 to 38 and 41 substantially as herein described.

44. A process as claimed in any one of claims 18, 19, 39, 40 and 42 substantially as herein described.

45. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 7.

46. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 10 to 17, 20 to 38, 41 and 43.

47. Compounds as claimed in claim 6 when prepared by a process as claimed in any of claims 18, 19, 39, 40, 42 and 44.

48. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as claimed in claim 1 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.



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49. Compositions as claimed in claim 48 in a form suitable for oral, parenteral or rectal administration.

50. Compositions as claimed in claim 48 or claim 49 in the form of tablets, coated tablets, capsules, solutions, syrups, emulsions, powders, suppositories or injection solutions.

51. Compositions as claimed in either of claims 48 and 49 in the form of dosage units.

52. Compositions as claimed in claim 51 wherein each dosage unit contains from 0.05 to 50 mg of the said active ingredient.

53. Compositions as claimed in claim 52 wherein each dosage unit contains from 0.1 to 25 mg of the said active ingredient.

54. Compositions as claimed in any of claims 48 to 53 which contain a spasmolytic or β -receptor blocker.

55. Pharmaceutical compositions as claimed in any of claims 48 to 54 which comprise as active ingredient at least one compound of formula I as claimed in claim 6 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

56. Compositions as claimed in claim 48 substantially as herein described.

57. Compositions as claimed in claim 55 substantially as herein described.

58. Pharmaceutical compositions substantially as herein described in any one of Examples A to C.

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