

1 497 527

PATENT SPECIFICATION

(11) 1 497 527

- (21) Application No. 27236/77 (22) Filed 3 March 1975
 (62) Divided Out of No. 1 490 269
 (31) Convention Application No. 2 435 041
 (32) Filed 20 July 1974
 (31) Convention Application No. 2 445 430
 (32) Filed 24 Sept. 1974
 (31) Convention Application No. 2 460 776
 (32) Filed 21 Dec. 1974 in
 (33) Fed. Rep. of Germany (DE)
 (44) Complete Specification published 12 Jan. 1978
 (51) INT CL³ C07D 495/00; A61K 31/55 (C07D 495/00, 207/16, 211/60, 211/78, 213/78, 243/08, 249/08, 307/24, 309/08, 333/26, 335/02)

(52) Index at acceptance

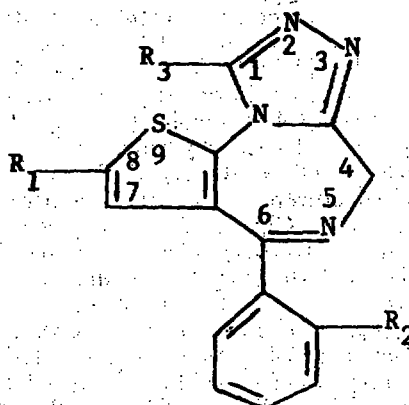
C2C 1173 1174 1175 1341 145X 1472 1510 1511 151X 1530
 1531 1532 1672 1712 200 214 215 220 221 225 226
 22Y 246 250 251 253 254 256 25Y 28X 29X 29Y 305
 30Y 311 313 314 31Y 327 337 338 351 354 364 36Y
 371 373 37Y 440 464 500 50Y 551 614 624 667 672
 677 69Y 740 759 770 776 77Y 790 79Y ME QL WC
 ZB ZF

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

(71) We, BOEHRINGER INGELHEIM G.M.B.H., 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, where appropriate, 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:—



(I)

(wherein

R₁ represents a hydrogen, chlorine or bromine atom or an alkyl group with 1 to 4 carbon atoms;

This Sheet Has Been Replaced





R_2 represents a hydrogen, fluorine, chlorine or bromine atom or a nitro or trifluoromethyl group; and

R_3 represents a chlorine or bromine atom, an alkoxy or alkylmercapto group with 1 to 3 carbon atoms, a cycloalkyl or cycloalkenyl group with 3 to 6 carbon atoms, a 5- or 6-membered saturated or unsaturated ring containing an oxygen, sulfur or nitrogen heteroatom said nitrogen heteroatom being optionally substituted by an alkyl group with 1 or 2 carbon atoms) and, where R_3 is other than a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring, 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.

Preferred compounds according to the present invention, by virtue of their favourable physiological activity, include compounds of formula I (as hereinbefore described) wherein R_1 represents a bromine atom, R_2 represents a chlorine or bromine atom and R_3 represents a bromine atom, a cycloalkyl group with 3 to 6 carbon atoms, a tetrahydropyranyl group, a tetrahydrothiopyranyl group or a piperidyl group optionally substituted by an alkyl group with 1 or 2 carbon atoms at the nitrogen atom. The piperidyl group is preferably substituted by a methyl group at the nitrogen atom.

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-cyclohexyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_6\text{H}_{11}$), 8-bromo-6-*o*-bromophenyl-1-cyclohexyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Br}$, $R_3 = \text{C}_6\text{H}_{11}$), 8-bromo-6-*o*-chlorophenyl-1-cyclobutyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_4\text{H}_7$), 8-bromo-6-*o*-chloropentyl-cyclopentyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_5\text{H}_9$), 8-bromo-6-*o*-chlorophenyl-1-cyclopropyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_3\text{H}_5$), 8-bromo-6-*o*-chlorophenyl-1-tetrahydropyranyl-(4)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_5\text{H}_{10}\text{O}$), 8-bromo-6-*o*-chlorophenyl-1-tetrahydropyranyl-(3)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_5\text{H}_{10}\text{O}$), 8-bromo-6-*o*-chlorophenyl-1-tetrahydrofuran-(2)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_4\text{H}_7\text{O}$), 8-bromo-6-*o*-bromophenyl-1-tetrahydrofuran-(2)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Br}$, $R_3 = \text{C}_4\text{H}_7\text{O}$), 8-bromo-6-*o*-chlorophenyl-1-[N-methylpiperidyl]-(3)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{CH}_3\text{-N-C}_5\text{H}_{10}$), 8-bromo-6-*o*-chlorophenyl-1-tetrahydrothiopyranyl-(2)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_5\text{H}_{10}\text{S}$), 1,8-dibromo-6-*o*-chlorophenyl-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{Br}$) and 8-bromo-6-*o*-chlorophenyl-1-methoxy-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine ($R_1 = \text{Br}$, $R_2 = \text{Cl}$, $R_3 = \text{OCH}_3$), and, where R_3 is other than a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring, the acid addition salts.



54

3

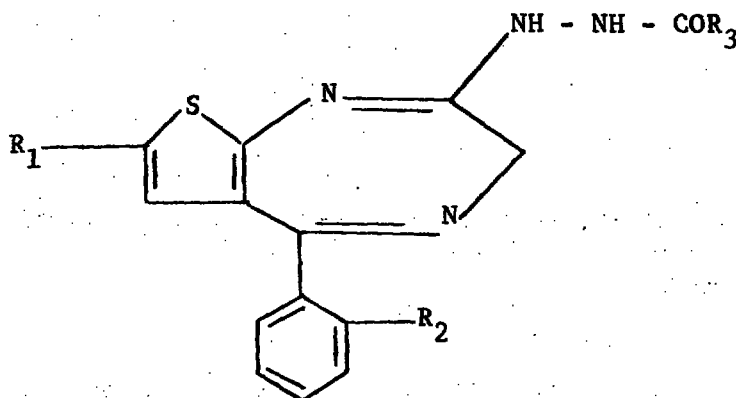
1,497,527

3

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

- 5 a) for the preparation of compounds of formula I as hereinbefore defined (wherein R_3 is other than a chlorine or bromine atom), the cyclization of a compound of the formula:—

5

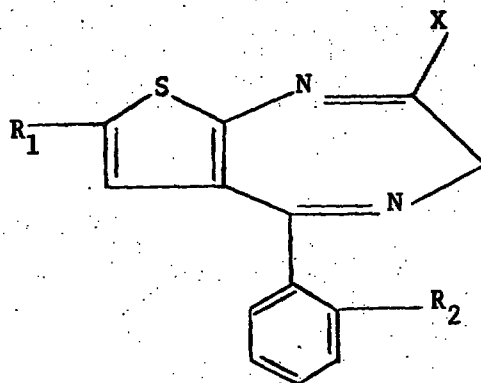


VII

- 10 (wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

10

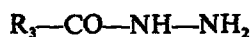
The compounds of formula VII are preferably first prepared by reacting a compound of the formula:—



II

- 15 (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:—

15



III

- 20 (wherein R_3 is as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula VII (as hereinbefore defined) is obtained.

20

- b) for the preparation of compounds of formula I as hereinbefore defined (wherein R_3 is other than a chlorine or bromine atom), the reaction of a compound of the formula:—

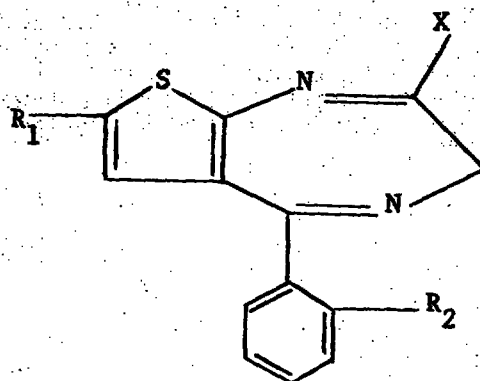


This Sheet Has Been Replaced



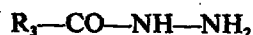
1,497,527

4



II

(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:—

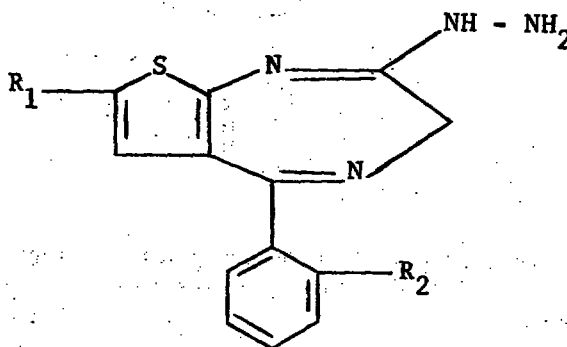


III

5 (wherein R_3 is as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

10 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 to 3 carbon atoms.

15 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:—



VII

25 (wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom). 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.

c) for the preparation of compounds of formula I as hereinbefore defined (wherein R_3 is other than a chlorine or bromine atom) the reaction of a compound of the formula:—

25

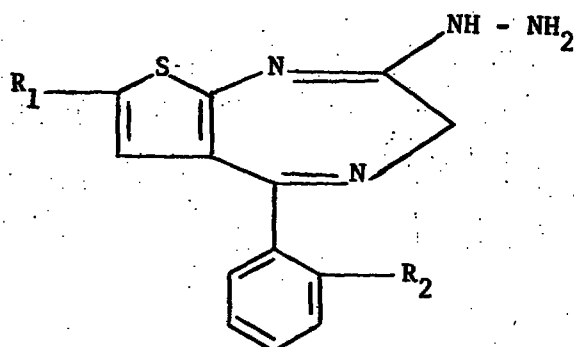


56

5

1,497,527

5



IV

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



V

5 (wherein R_3 is as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) or a reactive derivative thereof, whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

5

10 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 $R_3\text{---C(=NH)---OR'}$ (Vb), an amidine of general formula $R_3\text{---C(=NH)---NH}_2$ (Vc), an amide of general formula $R_3\text{---CONH}_2$ (Vd), a thioamide of general formula $R_3\text{---CSNH}_2$ (Ve), an ester of general formula $R_3\text{---COOR''}$ (Vf), an acid anhydride of general formula $(R_3\text{---CO})_2\text{O}$ (Vg), an acid halide of general formula $R_3\text{---COHal}$ (Vh) or a nitrile of general formula $R_3\text{---CN}$ (Vi) (in which R_3 is as hereinbefore defined with the proviso that it does not represent a chlorine or bromine atom, 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).

10

15

15

20

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:—

20



V



Vf



Vg

25



Vh

25



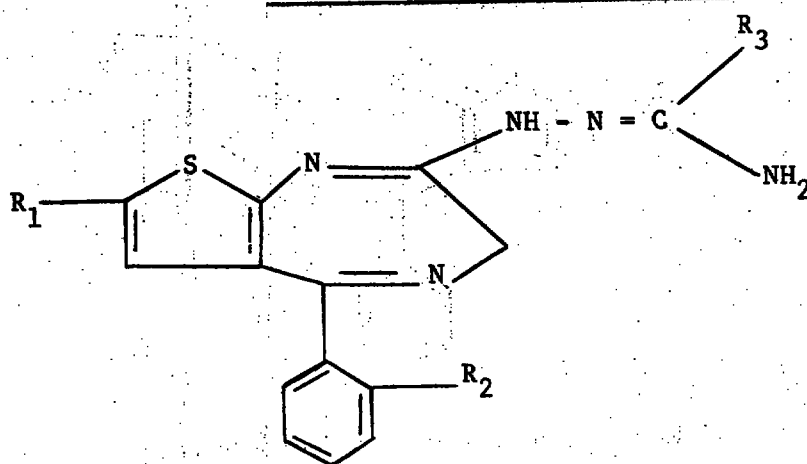
Vi

30

(wherein R_3 and R'' are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) 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.

30

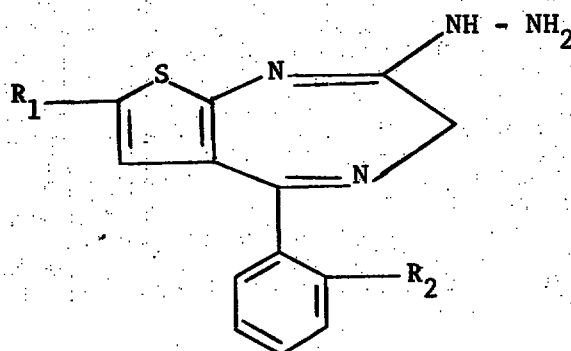
d) for the preparation of compounds of formula I as hereinbefore defined (wherein R_3 is other than a chlorine or bromine atom), the cyclization of a compound of the formula:—



VIII

(wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

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



IV

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



Vc

(wherein R_3 is as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom) 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:



58

7

1,497,527

7

Method I.

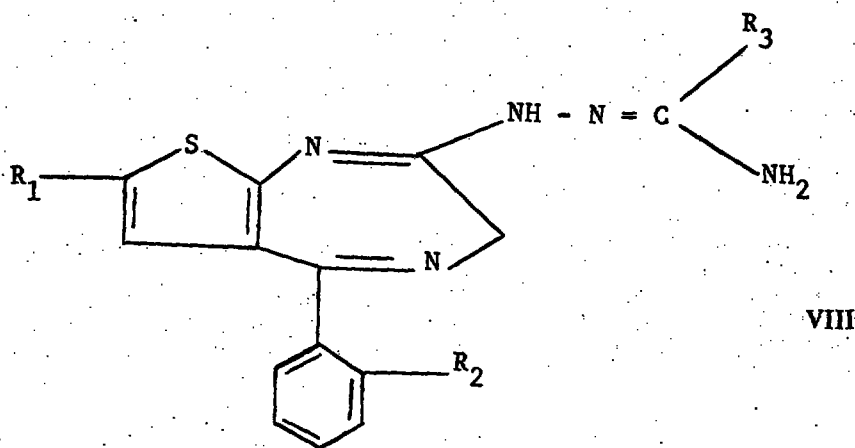
In this case the acid derivative of formula V is the orthoester $R_3-C(OR')_3$ (wherein R_3 and R' are as hereinbefore defined with the proviso that R_3 is other than a chlorine or bromine atom). Usually, the reaction is effected in the presence of an excess of the orthoester, serving simultaneously 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 with the proviso that R_3 is other than a chlorine or bromine atom). 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) with the proviso that R_3 is other than a chlorine or bromine atom. 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.

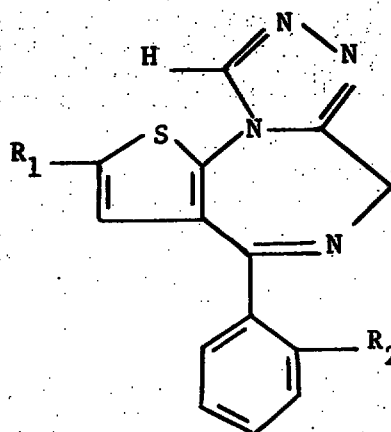
In this case the acid derivative of general formula V is an amide of thioamide of formula R_3-CONH_2 or R_3-CSNH_2 (wherein R_3 is as hereinbefore defined, but is other than a chlorine or bromine atom). The reaction may be effected either with or without a solvent and either with or without a catalyst 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 with the proviso that R_3 is other than a chlorine or bromine atom). The intermediate product of general formula VII is formed first, and may be cyclized as indicated for process (a).



e) for the preparation of compounds of formula I as hereinbefore defined (wherein R_3 represents a chlorine or bromine atom), the chlorination or bromination of a compound of the formula:—



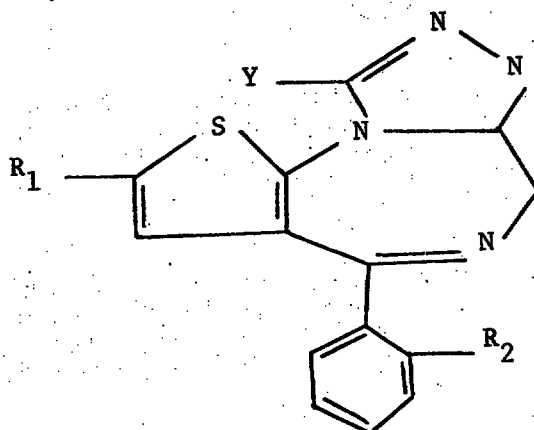
VI

(wherein R_1 and R_2 are as hereinbefore defined) whereby a compound of formula I (wherein R_3 represents a chlorine or bromine atom) is obtained.

For production of such final products of general formula I, where R_3 means a chlorine or bromine atom or a straight or branched alkoxy or alkylmercapto group with 1 to 3 carbon atoms, in line with process b, a compound of formula VI is brominated or chlorinated. Chlorination or bromination is preferably effected in a solvent such as carbon tetrachloride, chloroform, methylene chloride, dioxan, tetrahydrofuran, dimethylformamide or an appropriate hydrocarbon, optionally in the presence of a tertiary organic base such as pyridine, or a halosuccinimide. The temperature at which this reaction is effected is from room temperature to the reflux temperature of the reaction mixture, according to the starting material used and the method applied.

If desired, a 8-halogen compound may be converted into the corresponding alkoxy or alkylmercapto compound.

f) for the preparation of compounds of formula I as hereinbefore defined (wherein R_3 represents a straight or branched alkoxy or alkylthio group with 1 to 3 carbon atoms), the alkoxylation or alkylthiolation of a compound of the formula:—



VIa

(wherein R_1 and R_2 are as hereinbefore defined and Y represents a chlorine or bromine atom) to convert the compound of formula VIa into a compound of formula I (wherein R_3 represents a straight or branched alkoxy or alkylthio group with 1 to 3 carbon atoms).

60
9

9

1,497,527

Thus, for example the compound of formula VIa is reacted with an alkali metal alkoxide with 1 to 3 carbon atoms whereby a compound of formula I (wherein R_1 represents a straight or branched alkoxy group with 1 to 3 carbon atoms) is obtained. Alternatively, for example, the compound of formula VIa is reacted with an alkali metal alkylthio compound with 1 to 3 carbon atoms whereby a compound of formula I (wherein R_1 represents a straight or branched alkylthio group with 1 to 3 carbon atoms) is obtained.

An alkoxy group may, for example be introduced into the 8-halo compound by dissolving the halogen compound in an alkali metal alkoxide and refluxing the solution.

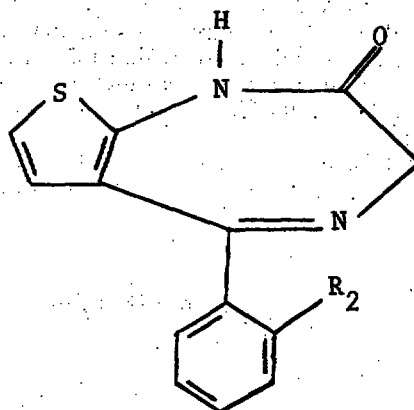
For the production of an alkylmercapto compound the 8-halo compound is preferably dissolved in an aprotic solvent such as dioxan, tetrahydrofuran, dimethylformamide or hexamethyl phosphorus triamide (HMPT) or in an alcohol and reacted with an alkali metal mercaptide; the alkali metal mercaptide may if desired be prepared *in situ*, e.g. by adding a mercaptan to a solution of the halogen-compound in the alkali metal alkoxide.

The final products of general formula I, other than compounds of formula I in which R_1 represents a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring, 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 formulae III and V are known from the literature. While production of the compounds of general formulae VI, VII and VIII has already been described, production of the compounds of general formulae II and IV is described in the following:

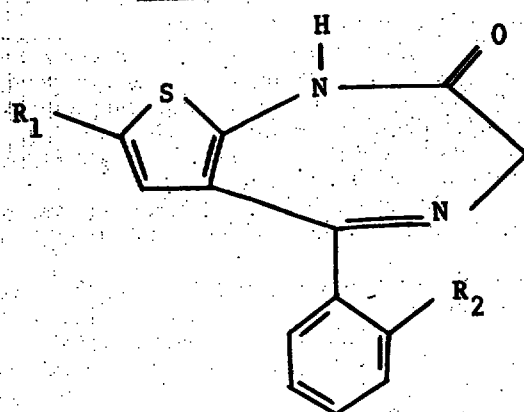
The hydrazine derivatives of general formula IV may, for example, be produced by reacting compounds of general formula II with hydrazine. This may, if desired, be effected in one of the above-mentioned solvents, one of the previously mentioned acid catalysts being present, if desired. The temperature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

The compounds of general formula II in which R_1 represents a halogen atom may, for example, be reacted either directly with compounds of general formula III to yield the final compounds of the 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 halogenating a compound of formula IX (which compounds are known from the literature)



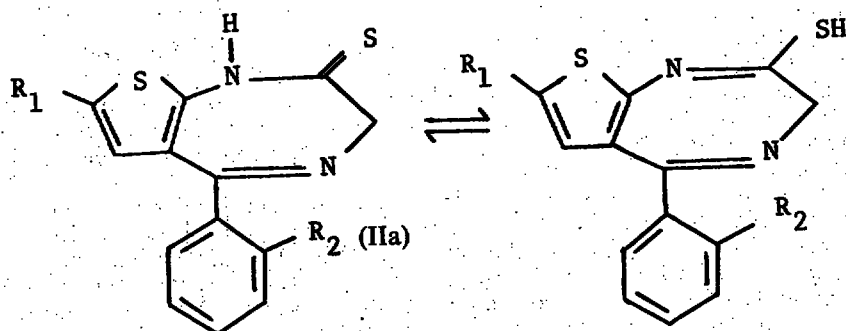
IX

(wherein R_2 is as hereinbefore defined) with chlorine, bromine, N-chloro- or N-bromo-succinimide or sulfonyl chloride in the conventional manner followed by reaction of the compounds obtained, of general formula:—



X

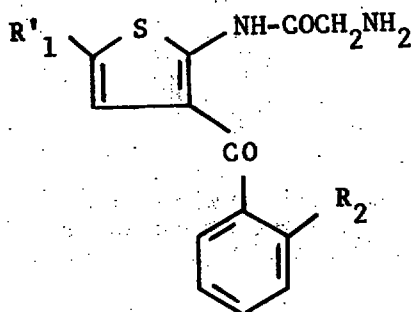
(wherein R_1 represents a halogen atom and R_2 is as hereinbefore defined) (certain of which compounds are known) with phosphorus pentasulfide, in the presence of a solvent such as pyridine, dimethylformamide or tetrahydrofuran or a mixture thereof. The reaction may be effected at a temperature of from room temperature to the reflux temperature of the reaction mixture. Compounds of general formula II in which X represents a $-SH$ group are thus obtained. The mercapto compounds are in tautomeric equilibrium with the corresponding thio compounds as shown in the following formula-scheme:



(IIb)

(wherein R_1 represents a halogen atom and R_2 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 thioalkyl group with 1 to 3 carbon atoms.

Compounds of general formulae IX and X (in which R_1 represents a bromine atom) may also be obtained by intramolecular cyclization of compounds of general formula:—

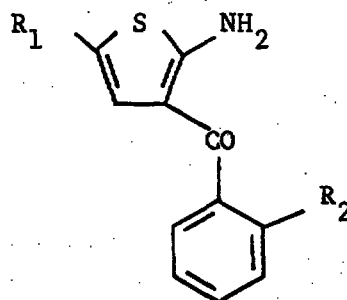


(XI)



wherein R_2 is as hereinbefore defined and R_1 represents a hydrogen or bromine atom. An especially advantageous variant if 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:—

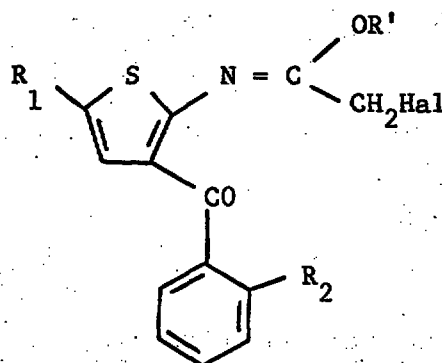


(XII)

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

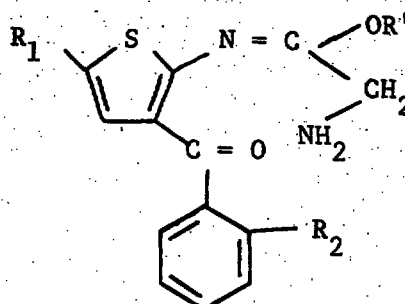


(wherein R' represents an alkyl group with 1—3 carbon atoms and Hal represents chlorine, bromine or iodine) to yield a compound of general formula:—



(XIV)

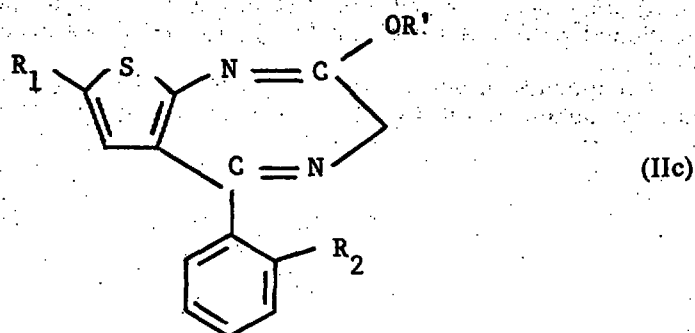
wherein R' , R_1 , R_2 and Hal are as hereinbefore defined. In a case where Hal represents a chlorine atom, it is useful to first exchange the aliphatically bound chlorine atom in the compound of general formula XIV by iodine, by means of a Finkelstein-reaction (e.g. by reacting with NaI in acetone).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



(XV)



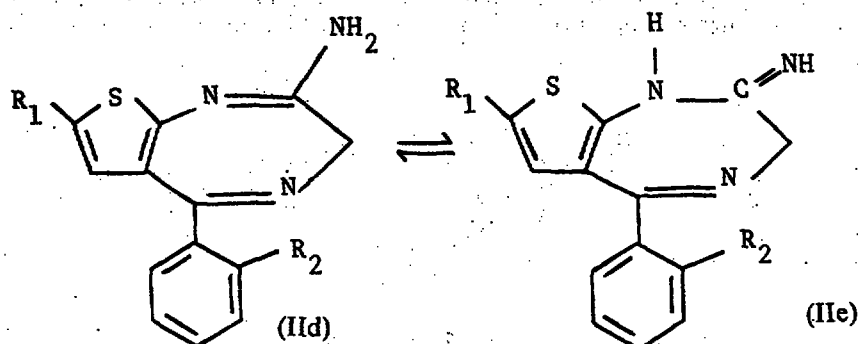
(wherein R_1 , R_2 and R_3 are as hereinbefore defined) is thus obtained as an intermediate, which, however, converts directly to a compound of the formula:



(wherein R_1 , R_2 and R_3 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 halogenation 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 formulation 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 (where R_3 is other than a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring) 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.



(64)

13

1,497,527

13

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, cyclamate, 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) 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-(ortho-chlorobenzoyl)-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 title compound 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.

I. Production Examples

Example 1.

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

a) 10 g of 8-bromo-6-(*o*-chlorophenyl)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine are dissolved in a mixture of 20 ml of pyridine and 100 ml of methylene chloride and heated for 7 hours. 6.3 g of bromine dissolved in 25 ml of methylene chloride are then added to the reaction mixture over the course of 5 minutes and the mixture is refluxed for a further 3 hours. Subsequently, the reaction mixture is cooled, diluted with methylene chloride and the solution shaken twice with 1 N hydrochloric acid and once with water. After drying, the methylene chloride solution is evaporated and the residue recrystallized from ethanol.

7.0 g = 60% of the title compound of m.p. 210—211°C are obtained.

b) the starting compound was obtained in the following way: 27 g of 7-bromo-5-(*o*-chlorophenyl)-2-hydrazino-3H-[2,3e]-thieno-1,4-diazepine of m.p. ~ 300°C (decomp.) are refluxed in a mixture of 23 ml of ethyl orthoformate and 300 ml of ethanol for 30 minutes. The solvent is evaporated off and the residue triturated with ether.

Yield: 26 g of m.p. 214—216°C.

Example 2.

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

12 g of 1,8-dibromo-6-(*o*-chlorophenyl)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine are refluxed in a solution of 0.6 g of sodium in 70 ml of methanol for 2 hours. Subsequently, the reaction mixture is evaporated, diluted with water and shaken repeatedly with methylene chloride. The methylene chloride phase is dried and the methylene chloride evaporated off. 7g = 76% of theory of the title compound of m.p. 198—200°C are obtained from the residue after recrystallization from ethanol.

Example 3.

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

0.15 g of sodium are dissolved in 40 ml of absolute methanol and 340 mg of methylmercaptan are introduced into the solution. The solution is then mixed with 2.5 g of 1,8-dibromo-6-(*o*-chlorophenyl)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine and heated to a temperature between 40 and 50°C. After approximately 30 minutes no dibromo compound was detectable by thin layer chromatography. The solution is then evaporated, the residue taken up in methylene chloride, the methylene chloride shaken with water several times, the organic base dried, the solvent evaporated and the residue chromatographed via a SiO₂-column.

920 mg = 40% of the title compound of m.p. 158—160°C are obtained.

Example 4.

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

a) 3.7 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione are dissolved in 40 ml of dioxan and refluxed with 4 g of cyclohexane carboxylic acid hydrazide for 30 minutes. After evaporation of the solvent the crystalline residue is treated with ether; 4.8 g of 7-bromo-5-(*o*-chlorophenyl)-2-cyclohexylcarbonylhydrazino-3H-[2,3e]-thieno-1,4-diazepine of m.p. 140°C (decomp.) are obtained.

66
15

15

1,497,527

b) 4.8 g of the hydrazino compound are heated to boiling with 150 ml of toluene and 25 g of SiO_2 for 3 hours in a water-separator. Subsequently, the title compound, which is insoluble, is filtered off with suction and eluted with methanol from the silica gel. 1.6 = 35% of theory of m.p. 179—180°C of the title compound are obtained.

Example 5.

1-Ethoxy-8-bromo-6-(*o*-chlorophenyl)-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine

3.7 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno[1,4]-diazepin-2-thione, 60 ml of *n*-butanol and 1g of *N*-ethoxycarbonylhydrazine are refluxed for 30 minutes. On cooling 2 g of the hydrazide of m.p. 236°C thus formed precipitate out. The crystals are filtered off with suction and boiled for 3 hours with 100 ml of xylene and 20 g of SiO_2 in a water-separator. The crystals are then filtered off such suction and the title compound eluted with methanol from the silica gel.

0.7 g = 37% of theory of m.p. 144—146°C are obtained.

Example 6.

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

a) 0.01 mol = 3.7 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione of m.p. 214°C (decomp) are refluxed with 50 ml of dioxan and 1.3 g of tetrahydrofuran-2-carboxylic acid hydrazine for 2 hours. It was found by a DC-control, that after this time the 7-bromo-5-(*o*-chlorophenyl)-2-tetrahydrofuran-yl-(2)-carbonyl-hydrazino-3H-[2,3e]-thieno-1,4-diazepine, formed as intermediate product according to the indicated reaction conditions, has already cyclized to yield the title compound.

The solvent is evaporated off and the residue chromatographed on SiO_2 , methylene chloride with 2% of methanol being used as eluting agent. After recrystallization from ethanol, 3.1 g = 66.2% of the title compound of m.p. 138—140°C are obtained.

b) 0.01 mol = 3.7 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione are refluxed in 50 ml of tetrahydrofuran with 1.3 g of tetrahydrofuran-2-carboxylic acid hydrazide for 3 hours. A dark-red solution is obtained. After evaporation off of the solvent the residue is crystallized out using a little ethanol. The crystals are filtered off with suction and washed with ether. In this manner 2.8 g = 59.7% of theory of 7-bromo-5-(*o*-chlorophenyl)-2-tetrahydrofuran-yl-(2)-carbonylhydrazino-3H-[2,3e]-thieno-1,4-diazepine of m.p. 199—200°C are obtained.

This compound is heated with 20 g of silica gel in 60 ml of xylene for 2 hours in a water separator. The xylene is decanted off and the title compound extracted from the silica gel several times with boiling methanol. The eluate is evaporated and the residue recrystallized from ethanol.

Yield: 2.0 g = 74.7% of theory of m.p. 140—142°C.

The 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione, used as starting compound, is obtained by heating the 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-one, known from the literature, with phosphorus pentasulfide in pyridine.

Example 7.

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

0.01 mol = 3.7 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione are refluxed with 80 ml of ethanol, 8 ml of pyridine and 1.5 g of tetrahydropyran-2-carboxylic acid hydrazide for 3 hours. Afterwards, the solvent is evaporated off and the residue triturated with cold ethanol.

3.5 g of 7-bromo-5-(*o*-chlorophenyl)-2-tetrahydropyran-yl-(2)-carbonylhydrazino-3H-[2,3e]-thieno-1,4-diazepine of m.p. 185°C are obtained.

This compound is heated in 60 ml of xylene with 20 g of silica gel for 2 hours on a water-separator. The xylene is decanted off and the title compound extracted from silica gel with boiling methanol. The eluate is evaporated and the residue recrystallized from ethanol.

1.9 g of the title compound of m.p. 211—212°C is obtained.



Example 8.

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

0.01 mol = 3.7 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione are suspended in 50 ml of tetrahydrofuran and mixed in portions with 0.5 g of a 50% sodium hydride dispersion in a commercial oil. The temperature is maintained at 20 to 25°C by ice-cooling. After 15 minutes 1 ml of methyl iodide is added and the reaction mixture is subsequently stirred for 30 minutes at 40°C. The solvent is evaporated off and the residue taken up in methylene chloride. The inorganic salts are washed with water. After evaporation of the solvent the crude methylmercapto compound is obtained.

3.2 g of this methyl compound are refluxed for 3 hours together with 1.2 g of tetrahydropyranyl-4-carboxylic acid hydrazide in 50 ml of methanol and nitrogen is simultaneously passed through the solution. The solvent is then evaporated off and to the residue are added 100 ml of xylene and 30 g of silica gel. The reaction mixture is heated for 3 hours on a water-separator in order to complete the cyclization reaction. Subsequently, the batch is processed as described in Example 6 b. After recrystallization from dioxan 3.4 g = 73% of theory of colourless crystals of m.p. 257—258°C are obtained.

Example 9.

8-Chloro-6-(*o*-chlorophenyl)-1-(tetrahydrofuran-2))-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine

0.01 mol = 3.25 g of 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3H-[2,3e]-thieno-1,4-diazepine, produced by reacting the corresponding thienodiazepinethione with hydrazine (m.p. 236°C decomp) are suspended in 100 ml of tetrahydrofuran and mixed with 1.0 ml of tetrahydrofuran-2-carboxylic acid chloride. The reaction mixture is refluxed for 5 hours, the solvent evaporated and further processed as described in Example 6a.

1.3 g = 32% of theory of colourless crystals of m.p. 191°C are obtained.

Example 10.

8-Bromo-6-(*o*-chlorophenyl)-1-[N-methylpiperidyl-(3)]-4H-s-triazolo-[3,4c]-thieno-[2,3e]-1,4-diazepine and its hydrochloride

a) 0.1 mol = 37.1 g of 7-bromo-5-(*o*-chlorophenyl)-3H-[2,3e]-thieno-1,4-diazepin-2-thione are dissolved or suspended in 300 ml of tetrahydrofuran and refluxed with 16 g of N-methylpiperidyl-3-carboxylic acid hydrazide (m.p. 83—85°C, gained from the corresponding ester with hydrazine) for 4 hours, nitrogen being passed through the solution continuously. After evaporation the residue is taken up in methylene chloride, washed with water, the solvent evaporated off and the residue crystallized out with ether.

42 g = 86% of theory of 7-bromo-5-(*o*-chlorophenyl)-2-[N-methyl-piperidyl-(3)]-carbonylhydrazino-3H-[2,3e]-thieno-1,4-diazepine of m.p. 208—209°C (decomp) are obtained.

b) 42 g of this latter compound are suspended in 1400 ml of xylene and mixed with 100 g of silica gel while stirring at a temperature of from 100 to 120°C. After heating on a water-separator for one hour, the reaction mixture is cooled, the solvent filtered off with suction and the title compound eluted from the silica gel with warm methanol.

16 g of colourless crystals of m.p. 240—241°C are obtained.

c) 10 g of the base are suspended in 20 ml of ethanol and mixed slowly with 20 ml of ethanolic hydrochloric acid. A solution is first formed then the hydrochloride crystallizes out. The hydrochloride is recrystallized from ethanol with the aid of charcoal and possesses a m.p. of 257 to 258°C (decomp.).

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



17

1,497,527

17

Example No.	R ₁	R ₂	R ₃	m.p. °C	Hydrazide of formula VII °C
11	Br	Cl		212-213	236(decomp)
12	Br	Cl	Cl	161-162	—
13	Br	Cl		190-191	110(decomp)
14	Br	Cl		192-193	oil
15	Cl	Cl	Br	170-172	—
16	Cl	Cl	OCH ₃	160-162	—
17	Cl	Cl		188-189	177 (decomp)
18	C ₂ H ₅	Cl		128-129	203
19	H	H		178-180	oil
20	H	Cl	Br	202-203	—
21	H	Cl	OCH ₃	184-185	—
22	C ₂ H ₅	Cl	Br	175-176	—
23	C ₂ H ₅	Cl	OCH ₃	oil	—
24	H	H	OCH ₃	167-168	—
25	H	H	Br	197-199	—
26	Br	Cl		145-147	—



Example No.	R ₁	R ₂	R ₃	m. p. °C	m. p. °C of Hydrazide
27	Br	Cl		190-191	212 (decomp)
28	Br	Cl		187-188	200 (decomp)
29	H	H		138-140 (1 Mol CH ₃ OH)	—
30	Br	Br		242	—
31	C ₂ H ₅	Cl		174-175	197 (decomp)
32	Br	Cl		171-180	217-218 (decomp)
33	Br	Cl		260-262	217 (decomp)
34	Br	Cl		251-253	196 (decomp)
35	Br	Cl		223-225	215-220 (decomp)
36	Br	Cl		187-189	197-198 (decomp)
37	Br	Cl		231-233	215-218 (decomp)
38	Br	Cl		209-211	213 (decomp)
39	Br	Cl		260-261	204-206
40	H	Cl		98-100	155 (decomp)
41	C ₂ H ₅	Cl		120-122	165-168 (decomp)
42	Br	Br		190-191	220 (decomp)
43	Br	Br		140-141	172 (decomp)



70

19

1,497,527

19

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	
	lactose	28.5 mg	
	corn starch	19.0 mg	
	gelatin	1.0 mg	
10	magnesium stearate	0.5 mg	10
		50.0 mg	

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 triturated 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: 100 mg.

20

Example B
Tablets

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

Production:

30 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.

35 Example C.
Suppositories

1 suppository consists of:

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

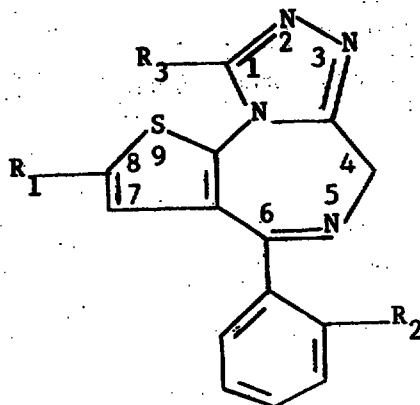
Production:

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:



(I)

(wherein

R_1 represents a hydrogen, chlorine or bromine atom or an alkyl group with 1 to 4 carbon atoms;

R_2 represents a hydrogen, fluorine, chlorine or bromine atom or a nitro or trifluoromethyl group; and

R_3 represents a chlorine or bromine atom, an alkoxy or alkylmercapto group with 1 to 3 carbon atoms, a cycloalkyl or cycloalkenyl group with 3 to 6 carbon atoms, a 5- or 6-membered saturated or unsaturated ring containing an oxygen, sulfur or nitrogen heteroatom said nitrogen heteroatom being optionally substituted by an alkyl group with 1 or 2 carbon atoms) and, where R_3 is other than a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring, the acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R_1 represents a bromine atom, R_2 represents a chlorine or bromine atom and R_3 represents a bromine atom, a cycloalkyl group with 3 to 6 carbon atoms, a tetrahydropyranyl group, a tetrahydrothiopyranyl group or a piperidyl group optionally substituted by an alkyl group with 1 or 2 carbon atoms at the nitrogen atom.

3. Compounds as claimed in claim 2 wherein R_3 represents a piperidyl group substituted by a methyl group at the nitrogen atom.

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

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

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

7. 8 - Bromo - 6 - (o - chlorophenyl) - 1 - cyclopentyl - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

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

9. 8 - Bromo - 6 - (o - chlorophenyl) - 1 - methoxy - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

10. 6 - (o - Chlorophenyl) - 1,8 - dibromo - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

11. 8 - Bromo - 6 - (o - chlorophenyl) - 1 - tetrahydrofuranyl - (2) - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

12. 8 - Bromo - 6 - (o - bromophenyl) - 1 - tetrahydrofuranyl - (2) - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

13. 8 - Bromo - 6 - (o - chlorophenyl) - 1 - tetrahydropyranyl - (4) - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

14. 8 - Bromo - 6 - (o - chlorophenyl) - 1 - tetrahydropyranyl - (3) - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

15. 8 - Bromo - 6 - (o - bromophenyl) - 1 - tetrahydropyranyl - (4) - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

16. 8 - Bromo - 6 - (o - chlorophenyl) - 1 - [N - methyl - piperidyl - (3)] - 4H - s - triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine and acid addition salts thereof.

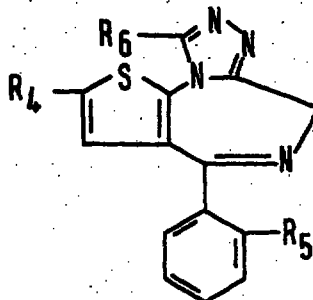




17. 8 - Bromo - 6 - (*o* - chlorophenyl) - 1 - tetrahydrothiopyranyl - (2) - 4H - s-triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine.

18. 8 - Bromo - 6 - (*o* - chlorophenyl) - 1 - tetrahydrothiopyranyl - (4) - 4H - s-triazolo - [3,4c] - thieno - [2,3e] - 1,4 - diazepine.

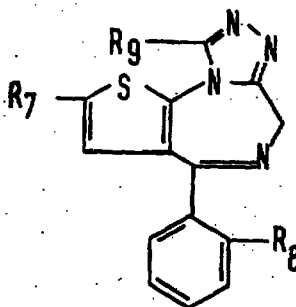
19. Compounds of the general formula:



Ia

(wherein R_4 represents a hydrogen, chlorine or bromine atom or an alkyl group with 1 to 4 carbon atoms; R_5 represents a fluorine, chlorine or bromine atom or a nitro or trifluoromethyl group; and R_6 represents a chlorine or bromine atom or an alkoxy or alkylmercapto group with 1 to 3 carbon atoms or a cycloalkyl or cycloalkenyl group with 3—6 carbon atoms) and the acid addition salts thereof.

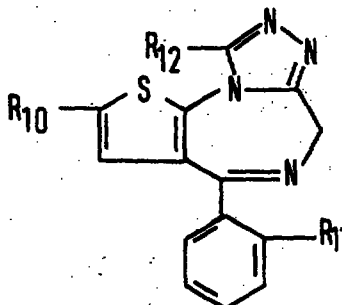
20. Compounds of the general formula:



Ib

(wherein R_7 represents a hydrogen, chlorine or bromine atom or an alkyl group with 1 to 4 carbon atoms; R_8 represents a hydrogen, fluorine, chlorine or bromine atom or a nitro or trifluoromethyl group; and R_9 represents a 5- or 6-membered ring containing an oxygen heteroatom) and the acid addition salts thereof.

21. Compounds of the general formula:



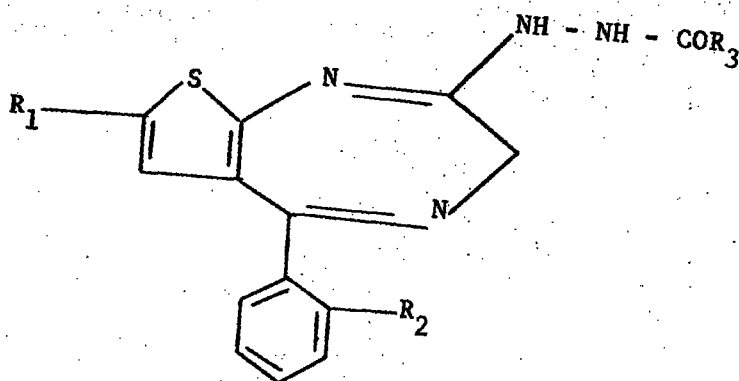
Ic

(wherein R_{10} represents a hydrogen, chlorine or bromine atom or an alkyl group with 1 to 4 carbon atoms, R_{11} represents a hydrogen, fluorine, chlorine or bromine atom or a nitro or trifluoromethyl group; and R_{12} represents a 5- or 6-membered ring containing a nitrogen or sulphur heteroatom, said nitrogen heteroatom being optionally substituted by an alkyl group with 1 or 2 carbon atoms) and where R_{12} is



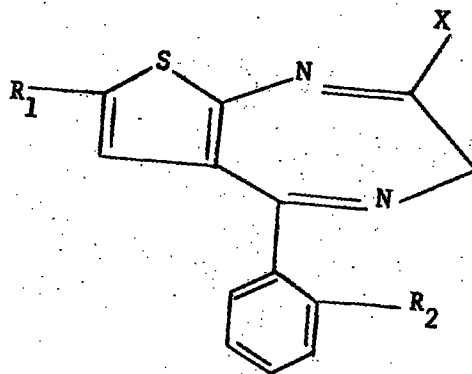


- other than a 5- or 6-membered ring containing a sulfur atom as a member in the ring, the acid addition salts thereof.
22. Compounds as claimed in any of claims 1—16 in the form of physiologically compatible acid addition salts.
23. Compounds as claimed in claim 19 in the form of physiologically compatible acid addition salts thereof.
24. Compounds as claimed in claim 20 in the form of physiologically compatible acid addition salts thereof.
25. Compounds as claimed in claim 21 in the form of physiologically compatible acid addition salts thereof.
26. Compounds as claimed in claim 1 other than as claimed in any of claims 4 to 18, as herein specifically disclosed.
27. Compounds as claimed in claim 19, other than as claimed in any of claims 4 to 10, as herein specifically disclosed.
28. Compounds as claimed in claim 20, other than as claimed in any of claims 11 to 15, as herein specifically disclosed.
29. Compounds as claimed in claim 21, other than as claimed in any of claims 16 to 18, as herein specifically disclosed.
30. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R_3 is other than a chlorine or bromine atom) which comprises cyclizing a compound of the formula:



VII

- (wherein R_1 , R_2 and R_3 are as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.
31. A process as claimed in claim 30 wherein the compound of formula VII is first prepared by reacting a compound of the formula:



II

- (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:



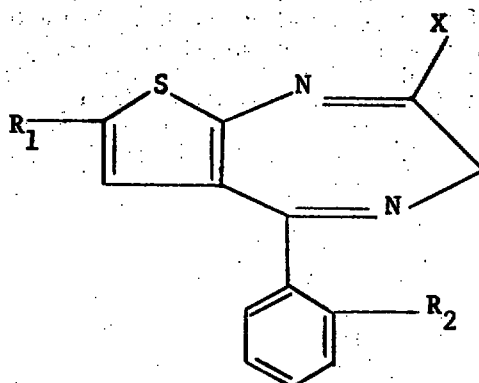
III





(wherein R_3 is as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula VII (as defined in claim 30) is obtained.

32. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R_3 is other than a chlorine or bromine atom) which comprises reacting a compound of the formula:



II

(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:



III

(wherein R_3 is as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

33. A process as claimed in claim 32 wherein a compound of formula II is used wherein X represents a halogen atom or a SH— or NH₂— group or an alkoxy or alkylmercapto group with 1 to 3 carbon atoms.

34. A process as claimed in any of claims 30 to 33 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.

35. A process as claimed in any of claims 30 to 34 wherein the cyclization and/or the reaction of the compounds of formulae II and III is effected in the presence of an acid catalyst.

36. A process as claimed in claim 35 wherein the acid catalyst comprises hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, acetic acid, propionic acid, benzenesulfonic acid or toluenesulfonic acids.

37. A process as claimed in any of claims 30 to 36 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.

38. A process as claimed in claim 30 and any of claims 34 to 37 for the preparation of compounds of formula Ia (wherein R_4 , R_5 and R_6 are as defined in claim 19 with the proviso that R_6 is other than a chlorine or bromine atom) wherein a compound of formula VII (wherein R_1 , R_2 and R_3 are as defined for R_4 , R_5 and R_6 in claim 19 with the proviso that R_6 is other than a chlorine or bromine atom) is cyclized.

39. A process as claimed in claim 30 and any of claims 34 to 37 for the preparation of compounds of formula Ib (as defined in claim 20) wherein a compound of formula VII (wherein R_1 , R_2 and R_3 are as defined for R_7 , R_8 and R_9 in claim 20) is cyclized.

40. A process as claimed in claim 30 and any of claims 34 to 37 for the preparation of compounds of formula Ic (as defined in claim 21) wherein a compound of formula VII (wherein R_1 , R_2 and R_3 are as defined for R_{10} , R_{11} and R_{12} in claim 21) is cyclized.

41. A process as claimed in any of claims 32 to 37 for the preparation of compounds of formula Ia (wherein R_4 , R_5 and R_6 are as defined in claim 19 with the proviso that R_6 is other than a chlorine or bromine atom) wherein a compound



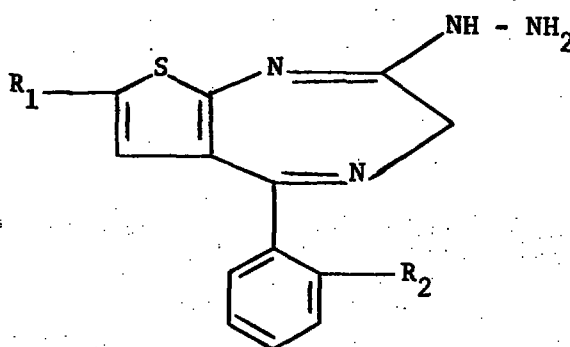


of formula II (wherein R_1 and R_2 are as defined for R_4 and R_5 in claim 19) is reacted with a compound of formula III (wherein R_3 is as defined for R_6 in claim 19 with the proviso that R_3 is other than a chlorine or bromine atom).

42. A process as claimed in any of claims 32 to 37 for the preparation of compounds of formula Ib (as defined in claim 20) wherein a compound of formula II (wherein R_1 and R_2 are as defined for R_4 and R_5 in claim 20) is reacted with a compound of formula III (wherein R_3 is as defined for R_6 in claim 20).

43. A process as claimed in any of claims 32 to 37 for the preparation of compounds of formula Ic (as defined in claim 21) wherein a compound of formula II (wherein R_1 and R_2 are as defined for R_{10} and R_{11} in claim 21) is reacted with a compound of formula III (wherein R_3 is as defined for R_{12} in claim 21).

44. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R_3 is other than a chlorine or bromine atom) which comprises reacting a compound of the formula:



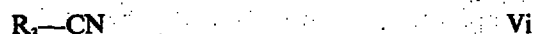
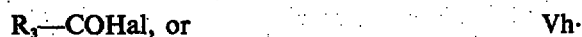
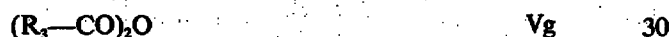
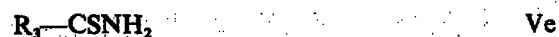
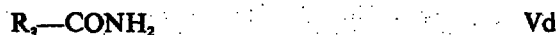
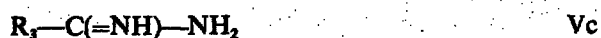
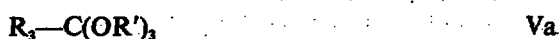
IV

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



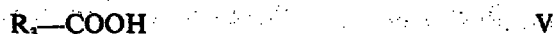
(wherein R_3 is as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) or a reactive derivative thereof, whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

45. A process as claimed in claim 44 wherein the reactive derivative of the compound of formula V is a compound of the formula:



(wherein R_3 is as defined in Claim 44, R' represents an alkyl group with 1-3 carbon atoms and R'' represents an aliphatic, araliphatic or aryl group).

46. A process as claimed in claim 30 wherein the compound of formula VII is first prepared by reacting a compound of formula IV (as defined in claim 44) with a compound of the formula:





26
25

25

1,497,527



Vf



Vg



Vh

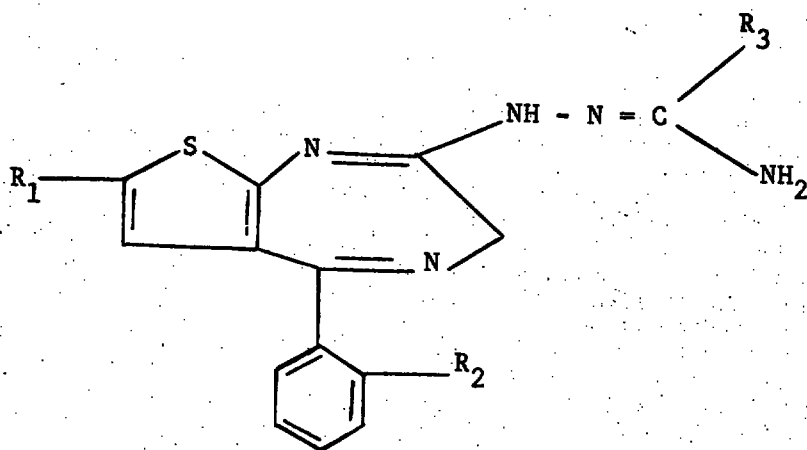


Vi

(wherein R_3 is as defined in claim 44 and R' and R'' are as defined in claim 45) whereby a compound of formula VII (as defined in claim 30) is obtained.

47. A process as claimed in claim 45 or claim 46 wherein a compound of formula Vh is used in which Hal represents a chlorine atom.

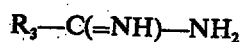
48. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R_3 is other than a chlorine or bromine atom) which comprises cyclizing a compound of the formula:—



VIII

(wherein R_1 , R_2 and R_3 are as defined in claim 1 with the provision that R_3 is other than a chlorine or bromine atom) whereby a compound of formula I (wherein R_1 , R_2 and R_3 are as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) is obtained.

49. A process as claimed in claim 48 wherein the compound of formula VIII is first prepared by reacting a compound of formula IV as defined in claim 44 with a compound of the formula:



Vc

(wherein R_3 is as defined in claim 1 with the proviso that R_3 is other than a chlorine or bromine atom) whereby a compound of formula VIII (as defined in claim 48) is obtained.

50. A process as claimed in claim 45 or claim 49 wherein the compound of formula Vb or Vc is used in the form of its salt with a mineral acid.

51. A process as claimed in claim 50 wherein the compound of formula Vb or Vc is used in the form of the hydrochloride salt.

52. A process as claimed in claim 45 wherein a compound of formula Vf is used in which R'' represents a methyl, ethyl or nitrophenyl group.

53. A process as claimed in any of claims 44 to 52 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.

54. A process as claimed in any of claims 44 to 53 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.

55. A process as claimed in claim 54 wherein the acid catalyst comprises hydrochloric acid, sulphuric acid, phosphoric acid, polyphosphoric acid, acetic acid, propionic acid, benzenesulphonic acid or toluenesulphonic acids.



* C L M S *



56. A process as claimed in any of claims 44 to 52 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.

57. A process as claimed in claim 56 wherein the base comprises 2-methylimidazole.

58. A process as claimed in any of claims 44 to 57 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.

59. A process as claimed in claim 58 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.

60. A process as claimed in claim 45 and claims 54 to 59 wherein the compound of formula IV (as defined in claim 44) is reacted with a molar excess of a compound of formula Va at a temperature of from 90 to 100°C.

61. A process as claimed in claim 45 or 49 wherein the compound of formula IV (as defined in claim 44) is reacted with a compound of formula Vc (as defined in claim 45) at a temperature of from 150 to 250°C and optionally in the presence of a basic catalyst.

62. A process as claimed in claim 49 wherein the reaction between the compound of formula IV (as defined in claim 44) and the compound of formula Vc (as defined in claim 45) 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.

63. A process as claimed in any of claims 44, 45 and 48 to 60 for the preparation of compounds of formula Ia (wherein R₄, R₅ and R₆ are as defined in claim 19 with the proviso that R₆ is other than a chlorine or bromine atom) wherein a compound of formula IV (wherein R₁ and R₂ are as defined for R₄ and R₅ in claim 19) is reacted with a compound of formula V (wherein R₃ is as defined for R₆ in claim 19 with the proviso that R₆ is other than a chlorine or bromine atom) or a reactive derivative thereof.

64. A process as claimed in any of claims 44, 45 and 48 to 60 for the preparation of compounds of formula Ib (as defined in claim 20) wherein a compound of formula IV (wherein R₁ and R₂ are as defined for R₇ and R₈ in claim 20) is reacted with a compound of formula V (wherein R₃ is as defined for R₉ in claim 20) or a reactive derivative thereof.

65. A process as claimed in any of claims 44, 45 and 48 to 60 for the preparation of compounds of formula Ic (as defined in claim 21) wherein a compound of formula IV (wherein R₁ and R₂ are as defined for R₁₀ and R₁₁ in claim 21) is reacted with a compound of formula V (wherein R₃ is as defined for R₁₂ in claim 21) or a reactive derivative thereof.

66. A process as claimed in any of claims 48 to 62 for the preparation of compounds of formula Ia (wherein R₄, R₅ and R₆ are as defined in claim 19 with the proviso that R₆ is other than a chlorine or bromine atom) wherein a compound of formula VIII (wherein R₁, R₂ and R₃ are as defined for R₄, R₅ and R₆ in claim 19 with the proviso that R₆ is other than a chlorine or bromine atom) is cyclized.

67. A process as claimed in any of claims 48 to 62 for the preparation of compounds of formula Ib (as defined in claim 20) wherein a compound of formula VIII (wherein R₁, R₂ and R₃ are as defined for R₇, R₈ and R₉ in claim 20) is cyclized.

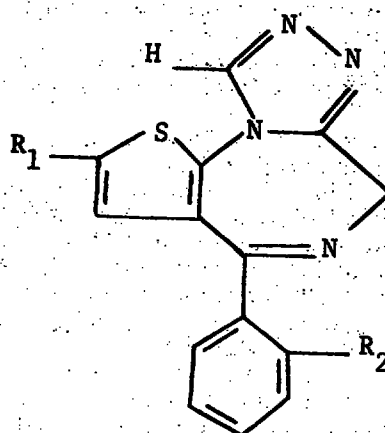
68. A process as claimed in any of claims 48 to 62 for the preparation of compounds of formula Ic (as defined in claim 21) wherein a compound of formula VIII (wherein R₁, R₂ and R₃ are as defined for R₁₀, R₁₁ and R₁₂ in claim 21) is cyclized.

69. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R₃ represents a chlorine or bromine atom) which comprises chlorinating or brominating a compound of the formula:—





78



VI

whereby a compound of formula I (wherein R_3 represents a chlorine or bromine atom) is obtained.

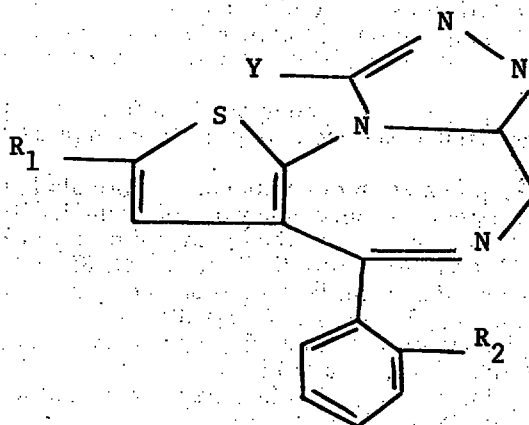
70. A process as claimed in claim 69 wherein the chlorination or bromination is effected in the presence of carbon tetrachloride, chloroform, methylene chloride, dioxan, tetrahydrofuran, dimethylformamide or an appropriate hydrocarbon as solvent.

71. A process as claimed in claim 69 or claim 70 wherein the chlorination or bromination is effected in the presence of a tertiary organic base or a halosuccinimide.

72. A process as claimed in claim 71 wherein the tertiary organic base is pyridine.

73. A process as claimed in any of claims 69 to 72 for the preparation of compounds of formula Ia as defined in claim 19 (in which R_6 represents a chlorine or bromine atom) wherein a compound of formula VI (wherein R_1 and R_2 are as defined for R_4 and R_5 in claim 19) is chlorinated or brominated.

74. A process for the preparation of compounds of formula I as defined in claim 1 (wherein R_3 represents a straight or branched alkoxy or alkylthio group with 1 to 3 carbon atoms) which comprises alkoxyating or alkylthiolating a compound of the formula:—



VIa

(wherein R_1 and R_2 are as defined in claim 1 and Y represents a chlorine or bromine atom) to convert the compound of formula VIa into a compound of formula I (wherein R_3 represents a straight or branched alkoxy or alkylthio group with 1 to 3 carbon atoms).

75. A process as claimed in claim 74 wherein the compound of formula VIa is reacted with an alkali metal alkoxide with 1 to 3 carbon atoms whereby a compound of formula I (wherein R_3 represents a straight or branched alkoxy group with 1 to 3 carbon atoms) is obtained.

76. A process as claimed in claim 74 wherein the compound of formula VIa is reacted with an alkali metal alkylthio compound with 1 to 3 carbon atoms whereby





a compound of formula I (wherein R_3 represents a straight or branched alkylthio group with 1 to 3 carbon atoms) is obtained.

77. A process as claimed in claim 76 wherein the alkali metal alkylthio compound is prepared *in situ* by reaction of a mercaptan with an alkali metal alkoxide.

78. A process as claimed in claim 76 or claim 77 wherein the reaction is effected in the presence of an aprotic solvent.

79. A process as claimed in claim 78 wherein the aprotic solvent comprises dioxan, tetrahydrofuran, dimethylformamide or hexamethyl phosphorus triamide.

80. A process as claimed in any of claims 74 to 79 for the preparation of compounds of formula Ia as defined in claim 19 (in which R_3 represents a straight chain or branched alkoxy or alkylmercapto group with 1 to 3 carbon atoms) wherein a compound of formula VIa (wherein R_1 and R_2 are as defined for R_1 and R_2 in claim 19) is alkoxylated or alkylthiolated.

81. A process as claimed in any of claims 30 to 37, 44 to 62, 69 to 72 and 74 to 79 wherein the compound of formula I (other than compounds of formula I wherein R_3 is a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring) thus obtained is converted into an acid addition salt thereof.

82. A process as claimed in any of claims 38, 41, 63, 66, 73 and 80 wherein the compound of formula Ia thus obtained is converted into an acid addition salt thereof.

83. A process as claimed in any of claims 39, 42, 64 and 67 wherein the compound of formula Ib thus obtained is converted into an acid addition salt thereof.

84. A process as claimed in any of claims 40, 43, 65 and 68 wherein any compound of formula Ic (in which R_{13} is other than a 5- or 6-membered ring containing a sulfur atom as a member in the ring) thus obtained is converted into an acid addition salt thereof.

85. A process as claimed in any of claims 30 to 37, 44 to 62, 69 to 72, 74 to 79 and 81 substantially as herein described.

86. A process as claimed in any of claims 38, 41, 63, 66, 73, 80 and 82 substantially as herein described.

87. A process as claimed in any of claims 39, 42, 64, 67 and 83 substantially as herein described.

88. A process as claimed in any of claims 40, 43, 65, 68 and 84 substantially as herein described.

89. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 43.

90. A process for the preparation of compounds of formula Ia (as defined in claim 19) substantially as herein described in any one of Examples 1 to 5 and 11 to 26.

91. A process for the preparation of compounds of formula Ib (as defined in claim 20) substantially as herein described in any one of Examples 6 to 9 and 27 to 31.

92. A process for the preparation of compounds of formula Ic (as defined in claim 21) substantially as herein described in any one of Examples 10 and 32 to 41.

93. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 32 to 37, 44 to 62, 69 to 72, 74 to 79, 81, 85 and 89.

94. Compounds as claimed in claim 19 when prepared by a process as claimed in any of claims 38, 41, 63, 66, 73, 80, 82, 86 and 90.

95. Compounds as claimed in claim 20 when prepared by a process as claimed in any of claims 39, 42, 64, 67, 83, 87 and 91.

96. Compounds as claimed in claim 21 when prepared by a process as claimed in any of claims 40, 43, 65, 68, 84, 88 and 92.

97. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as claimed in any of claims 1 to 18, 26 and 93 or (where R_3 is other than a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring) a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

98. Compositions as claimed in claim 97 in a form suitable for oral, parenteral or rectal administration.

99. Compositions as claimed in claim 97 or claim 98 in the form of tablets, coated tablets, capsules, solutions, syrups, emulsions, powders, suppositories or injection solutions.



80
29

29

1,497,527

100. Compositions as claimed in either of claims 97 and 98 in the form of dosage units.
- 5 101. Compositions as claimed in claim 100 wherein each dosage unit contains from 0.05 to 50 mg of the said active ingredient.
- 10 102. Compositions as claimed in claim 101 wherein each dosage unit contains from 0.1 to 25 mg of the said active ingredient.
103. Compositions as claimed in any of claims 97 to 102 which contain a further physiologically active ingredient.
- 10 104. Compositions as claimed in claim 103 wherein the further physiologically active ingredient is a spasmolytic or β -receptor blocker.
105. Pharmaceutical compositions as claimed in any of claims 97 to 104 which comprises as active ingredient at least one compound of formula Ia as claimed in any of claims 19, 27 and 94 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.
- 15 106. Pharmaceutical compositions as claimed in any of claims 97 to 104 which comprise as active ingredient at least one compound of formula Ib as claimed in any of claims 20, 28 and 95 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.
- 20 107. Pharmaceutical compositions as claimed in any of claims 97 to 104 which comprise as active ingredient at least one compound of formula Ic as claimed in any of claims 21, 29 and 96 or where R_{11} is other than a 5- or 6-membered saturated or unsaturated ring containing a sulfur atom as a member in the ring, a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.
- 25 108. Compositions as claimed in claim 97 substantially as herein described.
109. Compositions as claimed in claim 105 substantially as herein described.
110. Compositions as claimed in claim 106 substantially as herein described.
111. Compositions as claimed in claim 107 substantially as herein described.
- 30 112. Pharmaceutical compositions substantially as herein described in any of Examples A to C.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15-19 Kingsway,
London, WC2B 6UZ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.



* C L M S *

PATENTS ACT 1949

SPECIFICATION NO 1497527

The following corrections were allowed under Section 76 on 18 November 1980:

Page 1, heading (54) *for* [2, 3C] *read* [2, 3E]

THE PATENT OFFICE
14 January 1981

Bas 80297/1

(7)