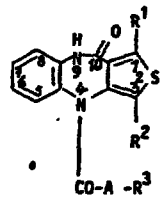
Substituted thienotricyclic compounds, processes for their preparation and medicaments containing them

The invention relates to substituted thienotricyclic compounds, processes for their preparation, their use and medicaments containing them.

The compounds according to the invention are used in the pharmaceuticals industry as intermediate products and for the preparation of medicaments.

An ulcer-inhibiting and secretion-inhibiting action is attributed to certain dibenzodiazepinones in German Offenlegungsschrift DE-OS 1,795,176. Substituted benzodiazepinones with an antidepressant and analgaesic action are known from U.S. Patent Specification US-PS 3,953,430. US-PS 4,168,269 describes substituted thienobenzodiazepinones with an analgaesic action. Thienobenzodiazepinones which have new interesting pharmacological actions have now been conceived.

The invention relates to substituted thienobenzodiazepinones of the general formula I



(I)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^3 denotes a halogen atom or the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group,

a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R^7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and their acid addition salts.

Alkyl radicals with 1 to 4 carbon atoms are the methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec.-butyl and tert.-butyl radical. Of the alkyl radicals, the methyl and ethyl radical are preferred for R^1, R^2, R^4, R^5, R^6 and R^7. The methyl radical is particularly preferred as the alkyl radical R^1 and R^2.

Alkenyl radicals with 3 to 5 carbon atoms which may be mentioned are the allyl radical and the 2-methyl-allyl radical.

Halogen atoms R^2 are the bromine atom and, in particular, the chlorine atom.

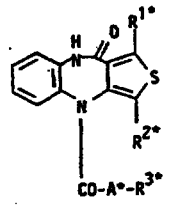
Halogen atoms R^3 (Hal) are the iodine and bromine atom and, in particular, the chlorine atom.

Alkylene groups with 1 to 5 carbon atoms are the trimethylene, tetramethylene, pentamethylene, propylene and ethylmethylene group, preferably the ethylene group and in particular the methylene group.

Possible salts are any desired acid addition salts. Salts which may be mentioned in particular are the pharmacologically acceptable salts of the inorganic and organic acids usually employed in galenics. Pharmacologically unacceptable salts are converted into pharmacologically acceptable salts by processes known to the expert. Examples of these which may be mentioned are water-soluble or water-insoluble acid addition salts, such as the hydrobromide, hydriodide, nitrate, acetate, benzoate, hibenzate [2-(4-hydroxybenzoyl)-benzoate], fendizoate (2-[(2'-hydroxy-4-biphenylyl)-carbonyl]-benzoate), propionate, butyrate, sulfosalicylate, laurate, oxalate, amsonate (4,4'-diaminostilbene-2,2'-disulfonate), embonate [4,4'-methylene-bis-(3-hydroxy-2-naphthoate)], metembonate (4,4'-methylene-bis-(3-methoxy-2-naphthoate)], stearate, 2-

hydroxy-3-naphthoate and 3-hydroxy-2-naphthoate, and in particular the hydrochloride, phosphate, sulfate, citrate, gluconate, maleate, malate, fumarate, succinate, tartrate, tosylate (p-toluenesulfonate), mesylate (methanesulfonate) and amidosulfonate.

Substituted thienobenzodiazepinones of the general formula I*



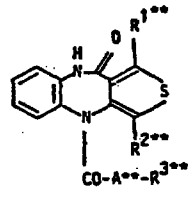
(I*)

wherein R^{1*} denotes a hydrogen atom or a methyl or ethyl radical, R^{2*} represents a chlorine atom or has one of the meanings of R^{1*}, R^{3*} denotes a chlorine atom and A* denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, form an embodiment of the invention.

Preferred representatives of embodiment I* are those in which R^{1*} denotes a hydrogen atom or a methyl radical, R^{2*} denotes a hydrogen atom or a methyl radical and A* denotes a methylene group.

Particularly preferred representatives of embodiment I* are those in which R^{1*} and R^{2*} denote a hydrogen atom, R^{3*} denotes a chlorine atom and A* denotes a methylene group.

Substituted thienobenzodiazepinones of the general formula I**



(I**)

wherein R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}, R^{3**} denotes the group $-N(R^{4**})R^{5**}$ and R^{4**} denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 4 carbon atoms and R^{5**}

has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}-N(R^{6**})R^{7**}$, or R^{4**} and R^{5**}, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^{6**} denotes a methyl or ethyl group, R^{7**} denotes a methyl or ethyl group, m** denotes 2 or 3 and A** denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, and their acid addition salts, form a further embodiment of the invention.

One group of representatives of embodiment I** comprises those in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{4**} denotes a methyl or ethyl radical and R^{5**} has the meaning of R^{4**} or represents the group $(CH_2)_{m**}-N(R^{6**})R^{7**}$, or R^{4**} and R^{5**}, together and including the nitrogen atom, denote a pyrrolidino, piperidino or hexahydroazepin-1-yl radical, and R^{6**} and R^{7**} denote a methyl or ethyl radical, m** denotes 2 and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts.

Another group of representatives of embodiment I** comprises those in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts.

Preferred representatives of embodiment I** are those in which R^{1**} denotes a hydrogen atom or a methyl radical, R^{2**} denotes a hydrogen atom or a methyl radical,

R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts.

Examples which may be mentioned of representatives of the compounds according to the invention are: 9,10-dihydro-4-[2-(di-n-propylamino)-propionyl]-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 4-[4-(di-n-butylamino)-butyryl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[2-(diethylamino)-propionyl]-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 4-[5-(diisopropylamino)-valeryl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[diisobutylaminoacetyl]-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[N-n-butyl-tert.-butylaminoacetyl]-9,10-dihydro-3-methyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 4-[4-(diallylamino)-butyryl]-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one, 4-[di-sec.-butylaminoacetyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[2-(N-ethyl-n-butylamino)-propionyl]-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 9,10-dihydro-3-methyl-4-[N-methyl-sec.-butylaminoacetyl]-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one, 9,10-dihydro-4-[5-(N-methyl-tert.-butylamino)-valeryl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 9,10-dihydro-4-[2-piperidinopropionyl]-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 4-[4-(hexahydroazepin-1-yl)-butyryl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodi-azepin-10-one, 4-[3-(di-n-butylamino)-propionyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[3-(diallylamino)-propionyl]-9,10-dihydro-4H-thieno[3,4-b]-[1,5]benzodiazepin-10-one, 4-[3-(di-sec.-butylamino)-propionyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[3-(N-n-butyl-tert.-butylamino)-propionyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[3-(N-ethyl-n-butylamino)-propionyl]-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 9,10-dihydro-4-[3-(N-methyl-sec.-butylamino)-propionyl]-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one, 9,10-dihydro-4-[3-piperidinopropion-

yl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 9,10-dihydro-1-methyl-4-[(4-methylpiperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and 4-[3-(hexahydroazepin-1-yl)-propionyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one and preferably 9,10-dihydro-4-[(4-methylpiperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 9,10-dihydro-1,3-dimethyl-4-[(4-methylpiperazin-1-yl)-acetyl]-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one and 9,10-dihydro-3-methyl-4-[4-methylpiperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, and their pharmacologically acceptable acid addition salts.

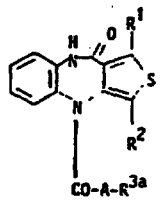
The substituted thienobenzodiazepinones of the general formula I and their acid addition salts and embodiments I* and I** have useful properties which render them commercially useful. The substituted thienobenzodiazepinones of the general formula I in which R^3 denotes the group $N(R^4)R^5$ and R^4 and R^5 have the abovementioned meanings, and those of embodiment I**, are characterized by an excellent protective action on the stomach and intestine in warm-blooded animals, and they inhibit, for example, the formation of gastric ulcers. They furthermore have a favourable therapeutic range, due to their low toxicity and the lack of substantial side effects. The substituted thienobenzodiazepinones of the general formula I in which R^3 denotes a halogen atom (Hal) and Hal has the abovementioned meaning, and those of embodiment I*, are useful intermediate products in the preparation of the pharmacologically active and therapeutically usable compounds according to the invention.

The excellent activity of the pharmacologically active substituted thienobenzodiazepinones and their pharmacologically, that is to say biologically, acceptable acid addition salts enable them to be used in human medicine and also in veterinary medicine, where they are employed for the treatment and prophylaxis of illnesses based on diseases of the stomach or intestine. For example, acute and chronic gastric ulcers and duodenal ulcers, gastritis or hyperacidic irritative stomachs are

treated in humans and animals.

The compounds according to the invention are therefore used in the treatment of mammals suffering from one of the abovementioned illnesses, a therapeutically active and pharmacologically acceptable amount of one or more compounds of the general formula I or I**, preferred representatives thereof and/or salts thereof being administered to the sick mammal. The invention thus also relates to the compounds according to the invention in their use for combating the abovementioned illnesses. The invention also includes the use of compounds according to the invention in the preparation of medicaments which are used for combating the illnesses mentioned.

The invention furthermore relates to medicaments containing one or more thienobenzodiazepinones of the general formula Ia



(Ia)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^{3a} denotes the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R^7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched

alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and/or their pharmacologically acceptable acid addition salts.

Embodiments of the medicaments are those which contain thienobenzodiazepinones of the formula I** or their preferred representatives and/or their pharmacologically acceptable acid addition salts.

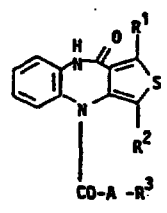
The medicaments are prepared by processes which are known per se. The compounds according to the invention are employed as medicaments either as such or, preferably, in combination with suitable pharmaceutical excipients. If the new pharmaceutical formulations contain pharmaceutical excipients in addition to the compounds according to the invention, the active compound content of these mixtures is 0.5 to 95, preferably 15 to 75, per cent by weight of the total mixture. The medicaments are formulated in doses suitable, for example, for oral, rectal or parenteral (intravenous, intramuscular or subcutaneous) administration, for example as tablets, coated tablets, capsules, suppositories or a measured amount by volume of a powder, granules, a solution, an emulsion or a suspension.

The daily dose for oral administration is in general between 0.01 and 5, preferably 0.05 and 2.5 and in particular 0.1 and 1.5 mg/kg of body weight for mammals, and is administered, if appropriate, in the form of several, preferably 1 to 3, individual doses, in order to achieve the desired results.

The pharmaceutical formulations preferably consist of the active compounds according to the invention and non-toxic, pharmaceutically acceptable medicament excipients, which are used as an admix or diluent in solid, semi-solid or liquid form or as a coating agent, for example in the form of a capsule, a tablet coating, a sachet or another container, for the therapeutically active constituent. An excipient can serve, for example, as an agent which promotes absorption of the medicament by the body, as a formulation auxiliary, as a sweetener, as a flavour correctant, as a dyestuff or as a preservative.

If the substituted thienobenzodiazepinones according to the invention and/or their pharmacologically acceptable acid addition salts are to be used for the treatment of the illnesses mentioned, the pharmaceutical formulations can also contain one or more pharmacologically active constituents of other groups of medicaments, such as antacids, for example aluminium hydroxide or magnesium aluminate; secretion inhibitors, such as H_2 blockers, for example cimetidine; gastric and intestinal therapeutics, for example metoclopramide, bromopride and tiapride; tranquillizers, such as benzodiazepines, for example diazepam; spasmolytics, for example bietamiverine and camylofin; anticholinergics, for example oxyphencyclimine and phencarbamide; glucocorticoids, such as prednisolone, fluocortolone and betamethasone; non-steroid antiinflammatories, such as arylacetic acids and -propionic acids, heteroarylacetic acids and -propionic acids, benzothiazinecarboxamide dioxides, pyrazolidinediones and quinazolinones, for example ibuprofen, naproxen, diclofenac, fenbufen, indometacin, lonazolac, sudoxicam, piroxicam, phenylbutazone, bumadizone calcium and proquazone; local anaesthetics, for example tetracaine and procaine; and if appropriate also enzymes, vitamins, amino acids etc.

The invention furthermore relates to a process for the preparation of the substituted thienobenzodiazepinones of the general formula I

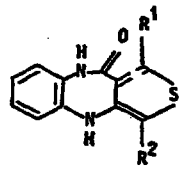


(I)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^3 denotes a halogen atom or the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings

of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R^7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and their acid addition salts.

The process is characterized in that thienobenzodiazepinones of the general formula II



(II)

wherein R^1 and R^2 have the abovementioned meaning, are acylated and, if appropriate, the products are then aminated and/or bases obtained are converted into acid addition salts or acid addition salts obtained are converted into the free base or pharmacologically acceptable acid addition salts.

The acylation and the amination which may then be carried out are effected by methods which are known per se.

For preparation of the thienobenzodiazepinones of the general formula I in which R^3 denotes -Hal, the starting compound of the formula II wherein R^1 and R^2 have the abovementioned meanings or their acid addition salts are reacted with compounds of the general formula III Hal-A-CO-Hal' (III) or IV $[Hal-A-CO]_2O$ (IV), wherein Hal' has one of the meanings of Hal and A and Hal have the abovementioned meanings. This acylation is carried out without or, preferably, in an inert solvent at room tem-

perature or an elevated temperature of not more than the boiling point of the solvent, if appropriate in the presence of an auxiliary base and/or an acylation catalyst. The acid halides III are preferable to the acid anhydrides IV. The preferred acid halide III is chloroacetyl chloride and the preferred acid anhydride IV is chloroacetic anhydride. Examples of solvents which may be mentioned are aromatic hydrocarbons, such as toluene, xylene or chlorobenzene; open-chain or cyclic ethers, such as diisopropyl ether or dioxane; chlorinated hydrocarbons, such as dichloroethane, and other solvents, such as pyridine, acetonitrile or dimethylformamide.

Examples of auxiliary bases which may be mentioned are tertiary organic bases, such as triethylamine and ethyl diisopropylamine, or pyridine; or inorganic bases, such as anhydrous alkali metal or alkaline earth metal carbonates or bicarbonates or alkaline earth metal oxides. Examples of possible acylation catalysts are imidazole, pyridine or 4-dimethylaminopyridine.

The process for the preparation of the intermediate products of the general formula I is thus characterized in that a thienobenzodiazpinone of the general formula II is acylated with compounds of the general formulae III or IV. Corresponding starting substances are used in the preparation of the intermediate products of the general formula I*.

To prepare the substituted thienobenzodiazepinones of the general formula I in which R^1, R^2 and A have the abovementioned meaning and R^3 denotes a group $-N(R^4)R^5$, the resulting reaction product of the formula I wherein R^3 denotes -Hal is reacted with secondary amines of the general formula V $HN(R^4)R^5$ (V), wherein R^4, R^5 and Hal have the above meaning.

The amination is carried out in an inert solvent at temperatures between 0^o and the boiling point of the solvent, either with at least 2 moles of secondary amine V or with 1 to 2 moles of secondary amine V and an auxiliary base. Examples of possible solvents are chlorinated hydrocarbons, such as methylene chloride, chloroform or

dichloroethane; open-chain or cyclic ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene, xylene, chlorobenzene or pyridine; alcohols, such as ethanol or isopropanol; ketones, such as acetone; and acetonitrile or dimethylformamide. Examples of auxiliary bases which may be mentioned are tertiary organic bases, such as triethylamine, N-methylpiperidine, diethylaniline or pyridine, or inorganic bases, such as alkali metal or alkaline earth metal carbonates or bicarbonates and alkaline earth metal hydroxides or oxides. If appropriate, the reaction can be accelerated by addition of alkali metal iodides. The reaction times are between 15 minutes and 80 hours, depending on the amount and nature of the amine V employed. In the case of reaction of starting compounds in which A represents an alkylene group with 2 to 5 carbon atoms, the reaction may also proceed with splitting off of H-Hal; the alkenyl compound intermediately formed, which can be isolated if appropriate, reacts with the secondary amine V to give the same end product.

To prepare the substituted thienobenzodiazepinones of the general formula I in which R^1, R^2 and A have the abovementioned meaning and R^3 denotes a group $-N(R^4)R^5$, alternatively, thienobenzodiazepinones of the general formula II wherein R^1 and R^2 have the abovementioned meaning are acylated with compounds of the general formula IX

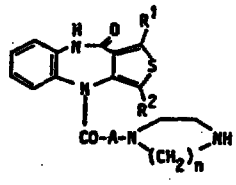
$$Z\text{-}CO\text{-}A\text{-}N(R^4)R^5 \qquad (IX)$$

wherein A, R^4 and R^5 have the abovementioned meanings and Z represents a detachable group (= leaving group).

The reaction of the compounds II with the acid derivatives IX is carried out in a manner which is known per se. The detachable group Z is a group which forms a reactive carboxylic acid derivative together with the carbonyl group to which it is bonded. Examples which may be mentioned of reactive carboxylic acid derivatives are acid halides, esters, anhydrides or mixed anhydrides, such

as are formed from salts of the corresponding acid (Z = OH) and acid chlorides, such as phosphorus oxychloride or chloroformic acid esters. The reaction is preferably carried out with the mixed anhydrides IX of strong mineral acids, in particular chlorophosphoric acid. If appropriate, the reaction is carried out in the presence of an acid-binding agent (proton acceptor). Examples of suitable proton acceptors which may be mentioned are alkali metal carbonates or bicarbonates, such as sodium carbonate or potassium bicarbonate; tertiary organic amines, such as pyridine, triethylamine or ethyl diisopropylamine; or sodium hydride. The reaction is carried out at temperatures between -25° and 50° in an inert solvent, preferably in dimethylformamide.

To prepare the substituted thienobenzodiazepinones of the general formula I in which R^1, R^2 and A have the abovementioned meaning and R^3 denotes a group $-N(R^4)R^5$, in which R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, alternatively, resulting piperazinylthienobenzodiazepinones of the general formula X



(X)

wherein R^1, R^2 and A have the abovementioned meaning and n denotes 2 or 3, are methylated or ethylated.

The methylation and the ethylation are carried out by processes which are known per se. Thus, examples of possible methylating and ethylating agents for compounds of the general formula X are: methyl and ethyl esters of strong acids, for example of sulfuric acid, phosphoric acid or p-toluenesulfonic acid, or methyl or ethyl halides, which are used between 0°C and 50°C, if appropriate in

the presence of a proton acceptor, in an aqueous or non-aqueous medium, such as is described, for example, in Houben-Weyl, Volume XI/1, page 24 et seq. and page 205 et seq., Georg-Thieme-Verlag, Stuttgart (1957); and mixtures of formaldehyde or acetaldehyde with a reducing agent (reductive alkyation method), possible reducing agents being nascent hydrogen (for example from zinc and hydrochloric acid), hydrogen in the presence of a hydrogenation catalyst, such as platinum or Raney nickel, formic acid or complex metal hydrides, such as sodium borohydride or sodium cyanoborohydride. Reductive alkylation methods are described in detail, for example, in Houben-Weyl, Volume XI/1, page 602 et seq., Georg-Thieme-Verlag, Stuttgart (1957); W.S. Emerson, Organic Reactions, Volume 4, page 174 et seq., John Wiley and Sons, New York (1948); M.L. Moore, ibid. Volume 5, page 301 et seq. (1949); C.A. Buehler, D.E. Pearson, Survey of Organic Synthesis, Volume 1, pages 424-429 (1970), Volume 2, 403-407 (1977), John Wiley and Sons, New York; and S.R. Sandler, W. Karo, Organic Functional Group Preparations, Volume 1, page 345 et seq. (1968), Academic Press, New York. The methylation is preferably carried out as reductive methylation.

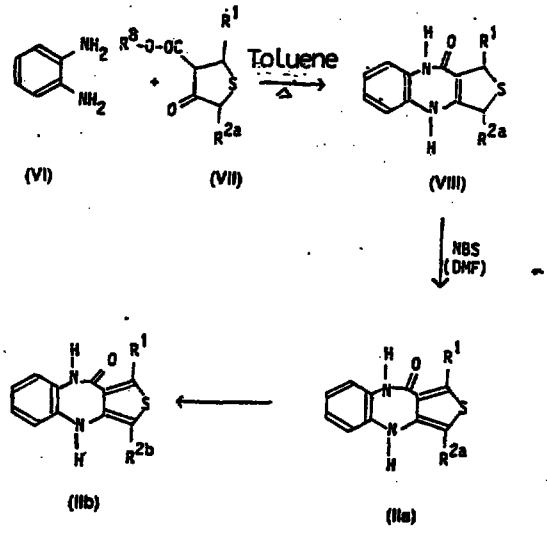
The process for the preparation of the pharmacologically active thienobenzodiazepinones of the general formula I is thus characterized in that compounds of the formula I wherein R^3 denotes -Hal are reacted with compounds of the general formula V, or in that thienobenzodiazepinones of the general formula II are acylated with acid derivatives IX, or in that compounds X are methylated or ethylated, and in each case, if appropriate, the base obtained is converted into a pharmacologically acceptable acid addition salt or an acid addition salt obtained is converted into the free base or a pharmacologically acceptable acid addition salt.

Acid addition salts are obtained by dissolving the free base obtained in a suitable solvent, for example water, acetone, an alkanol, such as ethanol or isopropanol, or an open-chain or cyclic ether, such as diethyl ether or tetrahydrofuran, which contains the desired acid or to

which the desired acid is subsequently added. The salts are isolated by filtration, precipitation with a non-solvent for the acid addition salt or by evaporation of the solvent. Salts can also be converted into other salts, for example pharmacologically acceptable acid addition salts, by conversion into the base and subsequent reaction with another acid.

The salts obtained can be converted, for example, into the free base by alkali treatment with aqueous sodium hydroxide or potassium hydroxide, and the base is then isolated by suitable measures, for example solvent extraction with a water-immiscible solvent, such as chloroform, diethyl ether or toluene.

The starting compounds of the general formula II are prepared in accordance with or analogously to the process in US-PS 3,953,430, by the following equation:

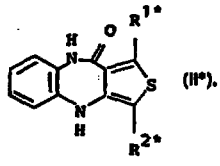


Phenylenediamine (VI) is reacted with tetrahydrothiophenecarboxylic acid derivatives VII in which R^1 has the abovementioned meaning and R^{2a} denotes a hydrogen atom or an alkyl group with 1 to 4 carbon atoms and R^8 denotes a hydrogen atom or an alkyl group with 1 to 5 carbon atoms, in inert solvents, for example toluene, with heating, to give the tetrahydrothienobenzodiazepinones VIII. The compounds VIII are dehydrogenated with a suitable dehydrogenating agent, for example N-bromosuccinimide in dimethylformamide, to give the dihydrothienobenzodiazepin-

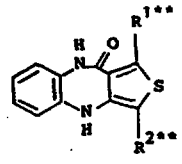
ones IIa. The representatives IIa in which R^{2a} denotes a hydrogen atom are converted into the halogen derivatives IIb in which R^{2b} denotes a chlorine or bromine atom by chlorination or bromination with suitable halogenating agents.

The compounds IX are known or can be prepared by known processes, if appropriate in situ. The piperazinothienobenzodiazepinones X are prepared by reaction of compounds of the formula I wherein R^3 denotes -Hal with corresponding amines V, that is to say piperazine or homopiperazine, by the methods described above for the amination.

To prepare the compounds I* or I**, corresponding starting compounds II*, II**, III*, III**, IV*, IV**, V**, IX** and X**



(II*),

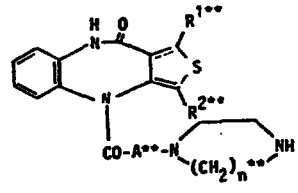


(II**)

$Cl\text{-}A^*\text{-}CO\text{-}Cl$ (III*), $Cl\text{-}A^{**}\text{-}CO\text{-}Cl$ (III**),

$(Cl\text{-}A^*\text{-}CO)_2O$ (IV*), $(Cl\text{-}A^{**}\text{-}CO)_2O$ (IV**),

$HN(R^{4**})R^{5**}$ (V**), $Z^{**}\text{-}CO\text{-}A^{**}\text{-}N(R^{4**})R^{5**}$ (IX**)



(X**)

wherein R^{1*} or R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2*} or R^{2**} represents a chlorine atom or has one of the meanings of R^{1*} or R^{1**}, A* or A** denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, R^{4**} denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 4 carbon atoms and R^{5**} has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}\text{-}N(R^{6**})R^{7**}$, or R^{4**} and R^{5**}, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group,

a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, R^{6**} denotes a methyl or ethyl group, R^{7**} denotes a methyl or ethyl group, m** denotes 2 or 3, n** denotes 2 or 3 and Z** denotes a detachable group, are employed.

The following examples serve to illustrate the invention in more detail. "m.p." denotes "melting point", "D." denotes "decomposition".

Example 1

3.5 g of 4-chloroacetyl-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 8.1 g of N-methylpiperazine and 50 ml of toluene are stirred at 80°C for 2 hours. 60 ml of dilute sodium hydroxide solution are added, the layers are separated, and the aqueous phase is extracted several more times by shaking with toluene and ... (sic) is concentrated to dryness in vacuo. The residue is made to crystallize with a little acetone. 4.2 g of 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b]-[1,5]benzodiazepin-10-one, m.p. 177-178°C (acetone) are obtained.

9,10-Dihydro-3-methyl-4-[(4-methyl-piperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 263-264°C (ethanol), 3-chloro-9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 239°C and 9,10-dihydro-1,3-dimethyl-4-[(4-methyl-piperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzo-diazepin-10-one, m.p. 204-205°C are obtained analogously by reaction of 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 3-chloro-4-chloro-acetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 4-chloroacetyl-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one with N-methyl-piperazine.

Example 2

14.9 g of 4-chloroacetyl-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 21 g of N-methylpipera-

zine and 70 ml of dioxane are stirred at 80°C for 1 hour and the solution is concentrated to dryness in vacuo. 150 ml of isopropanol and 40 ml of water are added to the residue, 25 ml of concentrated hydrochloric acid are added dropwise and the mixture is cooled in an ice-bath to give 9,10-dihydro-4-[(4-methylpiperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one dihydrochloride mixed with N-methylpiperazine hydrochloride. The hydrochlorides are dissolved in water and chloroform, the pH is brought to 8.2 with 2 N sodium hydroxide solution, the aqueous phase is extracted exhaustively by shaking with chloroform and the organic solution is dried and concentrated to dryness in vacuo. 16 g of 9,10-dihydro-4-[(4-methylpiperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 177-179°C (from acetone), are obtained.

9,10-Dihydro-4-(morpholinoacetyl)-4H-thieno[3,4-b]-[1,5]benzodiazepine-10-one, 4-[(4-benzylpiperazin-1-yl)-acetyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 4-[(4-ethylpiperazin-1-yl)-acetyl]-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and 4-[(2,4-dimethyl-piperazin-1-yl)acetyl]-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one are obtained analogously by reaction of 4-chloroacetyl-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one with morpholine, N-benzylpiperazine, N-ethylpiperazine or 1,3-dimethyl-piperazine.

Example 3

1.9 g of 4-chloroacetyl-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 0.55 g of pyrrolidine, 0.85 g of ground sodium carbonate and 15 ml of absolute ethanol are heated at the boiling point for 2 hours and the hot solution is filtered and concentrated in vacuo. The residue is dissolved in methylene chloride and the organic solution is washed at pH 7 with water and concentrated to give 1.4 g of 9,10-dihydro-4-(pyrrolidinoacetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one.

Example 4

1.9 g of 4-chloroacetyl-9,10-dihydro-4H-thieno-

[3,4-b][1,5]benzodiazepin-10-one, 3.7 g of piperidine and 15 ml of dioxane are stirred at 80°C for 1 hour, the mixture is concentrated in vacuo and the residue is recrystallized from isopropanol/water. 2.0 g of 9,10-dihydro-4-(piperidin-1-yl-acetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one are obtained.

9,10-Dihydro-3-methyl-4-(piperazin-1-yl-acetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 225-228°C, D.) is obtained analogously by reaction of 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one with piperazine; 9,10-dihydro-1,3-dimethyl-4-(morpholin-4-yl-acetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 188-190°C) is obtained analogously by reaction of 4-chloroacetyl-9,10-dihydro-1,3-dimethyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one with morpholine; and 9,10-dihydro-1,3-dimethyl-4-(piperidin-1-yl-acetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 162-164°C) is obtained analogously by reaction of 4-chloroacetyl-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one with piperidine.

Example 5

2.0 g of 4-chloroacetyl-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, 6 ml of 40% strength aqueous dimethylamine solution and 10 ml of methylene chloride are stirred at 35°C for 2 hours, 0.35 g of sodium carbonate is added and the mixture is concentrated to dryness in vacuo. A little water is added, the solution is extracted repeatedly by shaking with chloroform and the organic solution is dried with sodium sulfate and concentrated to dryness. 1.9 g of 4-(dimethylaminoacetyl)-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one are obtained.

4-(Diethylaminoacetyl)-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 196-197°C (from toluene) and 4-(diethylaminoacetyl)-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 186-187°C (from toluene) are obtained analogously by reaction of 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 4-chloroacetyl-

9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and diethylamine.

Example 6

9,10-Dihydro-3-methyl-4-(pyrrolidinoacetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 3-chloro-9,10-dihydro-4-(pyrrolidinoacetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and 9,10-dihydro-1,3-dimethyl-4-(pyrrolidinoacetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one are obtained analogously to Example 4 by reaction of 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 3-chloro-4-chloroacetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 4-chloroacetyl-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one with pyrrolidine.

Example 7

4-(Dimethylaminoacetyl)-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 3-chloro-4-(dimethylaminoacetyl)-9,10-dihydro-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one and 4-(dimethylaminoacetyl)-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one are obtained analogously tO Example 5 by reaction of 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one, 3-chloro-4-chloroacetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 4-chloroacetyl-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one with dimethylamine.

Example 8

8 g of 9,10-dihydro-3-methyl-4H-thieno[3,4-b]-[1,5]benzodiazepin-10-one and 5.6 ml of chloroacetyl chloride in 160 ml of dioxane are boiled under reflux in the presence of 8 g of ground potassium carbonate for 8 hours. The solution is concentrated to dryness, the residue is taken up in toluene, the mixture is washed with sodium bicarbonate solution and then with water and the toluene solution is dried over sodium sulfate. Concentration gives 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, m.p. 156-158°C.

3-Chloro-4-chloroacetyl-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, m.p. 214-216°C and 4-

chloroacetyl-9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b]-[1,5]benzodiazepin-10-one, m.p. 192-195°C, are obtained analogously by reaction of 3-chloro-9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one or 9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one with chloroacetyl chloride.

Example 9

10.4 ml of chloroacetyl chloride are added dropwise to a suspension of 18.8 g of 9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one in 500 ml of dioxane at room temperature, a clear solution being formed. The solution is left to stand for 3 hours and is concentrated to dryness, the residue is taken up in toluene, the mixture is washed with sodium bicarbonate solution and then with water and the toluene solution is dried over sodium sulfate. Concentration gives 4-chloroacetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one as an oil which slowly crystallizes. m.p. 220°C.

4-Chloroacetyl-9,10-dihydro-1-methyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one and 4-chloroacetyl-9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 156-158°C, are obtained analogously by reaction of 9,10-dihydro-1-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one with chloroacetyl chloride.

Example 10

2.2 g of chloroacetyl chloride and 2 ml of triethylamine are simultaneously added dropwise to a boiling solution of 2.2 g of 9,10-dihydro-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one in 30 ml of absolute dioxane in the course of 40 minutes, and stirring is continued for 3 hours. The mixture is allowed to cool and is filtered, the filtrate is concentrated to dryness, the residue is chromatographed over a silica gel column by means of a mixture of petroleum ether/ethyl acetate (1:1) and the product is recrystallized from toluene to give 2.0 g of 4-chloro-acetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one as an oil which slowly crystallizes, m.p. 220°C.

Example 11

A solution of 5 ml of sulfuryl chloride in 100 ml of methylene chloride is added dropwise to a solution of 12 g of 4-chloroacetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one in 300 ml of methylene chloride at 20°C. The mixture is left to stand at room temperature for 12 hours and is then extracted with sodium bicarbonate solution and washed with water. The .... (sic) phase is dried and concentrated. The residue is made to crystallize with a little methanol. 7 g of 3-chloro-4-chloroacetyl-9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 214-216°C (acetonitrile), are obtained.

Example 12

A mixture of 1.00 g of (4-methylpiperazin-1-yl)-acetic acid and 0.20 g of 75 per cent strength sodium hydride (in paraffin oil) in 16 ml of dimethylformamide is warmed at 50-80°C until the evolution of hydrogen has ended (2 to 3 hours). 1.35 g of 9,10-dihydro-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one are added to the sodium salt formed from the acid and 0.99 g of 98% pure phosphorus oxychloride is added dropwise at -10°C in the course of 10 minutes. The mixture is stirred at -10°C for 4 hours, at 0°C for 4 hours and at room temperature for 20 hours. It is poured onto ice, the pH is brought to 3.5 with sodium hydroxide solution, the mixture is extracted by shaking with methylene chloride and the aqueous phase is brought to pH 9 and extracted again by shaking with methylene chloride. The organic phase is washed with water and concentrated in vacuo. 0.6 g of 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 177-178°C (from acetone), is obtained.

9,10-Dihydro-3-methyl-4-[(4-methyl-piperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 263-264°C) and 9,10-dihydro-1,3-dimethyl-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 204-205°C) are obtained analogously by reaction of (4-methylpiperazin-1-yl)-acetic acid with sodium hydride, 9,10-dihydro-3-methyl-4H-thieno[3,4-b]-

[1,5]benzodiazepin-10-one or 9,10-dihydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and phosphorus oxychloride.

Example 13

1.1 g of ethyl chloroformate are added dropwise to a suspension of 1.58 g of (4-methylpiperazin-1-yl)-acetic acid in 20 ml of tetrahydrofuran. 2.18 g of 9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one are added to the suspension formed and the mixture is stirred at 0°C for a further hour and then at room temperature for 4 hours. It is poured onto 160 ml of 2 N sodium hydroxide solution and extracted with toluene and the organic phase is concentrated to dryness. Purification by column chromatography (silica gel; dioxane/methanol 1:1) gives 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 177-179°C.

9,10-Dihydro-3-methyl-4-[(4-methyl-piperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 263-264°C) is obtained analogously by reaction of 9,10-dihydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one with (4-methylpiperazin-1-yl)-acetic acid and ethyl chloroformate.

Example 14

2.0 g of 9,10-dihydro-3-methyl-4-(piperazin-1-yl-acetyl)-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 1.3 g of 98% strength formic acid and 0.3 g of 35% strength aqueous formaldehyde solution are warmed at 100-105°C for 2 hours, the mixture becoming liquid, with evolution of gas. The mixture is concentrated in vacuo, the residue is diluted with water, the pH is brought to 3.5 with dilute hydrochloric acid and the mixture is extracted by shaking with methylene chloride. The aqueous phase is brought to pH 9 and extracted with methylene chloride. The organic phase is washed, dried and concentrated. Recrystallization of the residue from methanol gives 9,10-dihydro-3-methyl-4-[(4-methyl-piperazin-1-yl)-acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 263-264°C.

The starting compounds are obtained in the follow-

ing manner:

Example A: 13.5 g of sulfuryl chloride in 100 ml of methylene chloride are added dropwise to a solution of 21.6 g of 9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepin-10-one in 300 ml of methylene chloride at -40°C. The mixture is left to stand at room temperature for a further hour, extracted by shaking with sodium bicarbonate solution and washed with water and the organic phase is dried and concentrated. The residue is made to crystallize with a little methanol. 3-Chloro-9,10-dihydro-4H-thieno[3,4-b]-[1,5]benzodiazepin-10-one is obtained.

Example B: 10 g of 1,3,9,10-tetrahydro-3-methyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one and 8.2 g of N-bromosuccinimide are dissolved in 250 ml of dimethylformamide. After one hour, the solution is poured onto 2 l of water. The precipitate is filtered off with suction and dissolved with hot toluene and the solution is clarified with Tonsil®. On cooling, 9,10-dihydro-3-methyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one, m.p. 228-230°C (methanol) is obtained as a precipitate.

9,10-Dihydro-1-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and 9,10-dihydro-1,3-dimethyl-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one (m.p. 195-196°C) are obtained analogously by dehydrogenation of 1,3,9,10-tetrahydro-1-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 1,3,9,10-tetrahydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one with N-bromosuccinimide.

Example C: 49.9 g of o-phenylenediamine and 80 g of 5-methyl-tetrahydro-4-oxo-3-thiophenecarboxylic acid are boiled in 4.5 l of toluene. The water formed is distilled off azeotropically with 2 l of the solvent in the course of 7 hours. The solvent is removed. 1,3,9,10-Tetrahydro-3-methyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, m.p. 195-197°C (isopropanol) is obtained.

1,3,9,10-Tetrahydro-1-methyl-4H-thieno[3,4-b][1,5]-benzodiazepin-10-one and 1,3,9,10-tetrahydro-1,3-dimethyl-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (m.p. 148-150°C) are obtained analogously by reaction of tetrahydro-2-methyl-4-oxo-3-thiophenecarboxylic acid or tetrahydro-2,5-

dimethyl-4-oxo-3-thiophenecarboxylic acid with o-phenylenediamine.

The following examples describe the formulation of the compound according to the invention to give medicaments.

Example 15

10,000 tablets with an active compound content of 20 mg are prepared from the following constituents:

200 g of 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one, 900 g of maize starch, 500 g of lactose, 30 g of amorphous silicic acid and 40 g of sodium lauryl-sulfate are mixed and the mixture is sieved. This mixture is moistened with a solution of 50 g of polyvinylpyrrolidone (average molecular weight 25,000) in 320 ml of alcohol and is granulated through a sieve of mesh width 1.25 mm. The granules are dried at 40° and mixed with 160 g of pectin, 100 g of talc and 20 g of magnesium stearate. This mixture is pressed to tablets of 200 mg with a diameter of 8 mm.

Example 16

100,000 capsules with an active compound content of 30 mg are prepared from the following constituents:

3,000 g of 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one are mixed with 5,000 g of neutral oil (Miglyol® 812) and soft gelatin capsules are filled with the mixture.

Example 17

100,000 capsules with an active compound content of 30 mg are prepared from the following constituents:

1,500 g of 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one and 1,500 g of magnesium trisilicate are mixed with 5,000 g of neutral oil (Miglyol® 812) and soft gelatin capsules are filled with the mixture.

Corresponding medicaments are obtained analogously to Examples 15 to 17 by using 9,10-dihydro-3-methyl-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one or 9,10-dihydro-1,3-dimethyl-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-

10-one instead of 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one.

Pharmacology

The excellent protective action of the pharmacologically active substituted thienobenzodiazepinones on the stomach can be demonstrated by the model of the so-called Shay rat. In this test, the compounds according to the invention prove to be clearly superior to the known commercial product carbenoxolone (1) in their protective action on the stomach and their therapeutic range, as can be demonstrated, for example, by comparison of (1) and 9,10-dihydro-4-[(4-methyl-piperazin-1-yl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10-one (2), 3-chloro-9,10-dihydro-4-[(4-methylpiperazin-1-yl)acetyl]-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one (3), 9,10-dihydro-3-methyl-4-[(4-methylpiperazin-1-yl)acetyl]-4H-thieno[3,4-b]-[1,5]benzodiazepin-10-one (4) and 9,10-dihydro-1,3-dimethyl-4-[(4-methylpiperazin-1-yl)acetyl]-4H-thieno-[3,4-b][1,5]benzodiazepin-10-one (5).

Table I

Anti-ulcerogenic action and toxicity of thienobenzodiazepinones

Serial No.	Toxicity LD_{50} [mg/kg] i.v. Mouse	Protective action on the stomach ED_{50} [mg/kg] p.o. Rat	TQ LD_{50}/ED_{50}	Gastric secretion +) % inhibition Rat
1	290	$\sim$ 70	4.1	7
2	190	2.5	76	35
3	75	$\lesssim$ 1	$\gtrsim$ 75	28
4	130	$\sim$ 0.3	$\sim$433	20
5	180	1.3	139	17

ED_{50} = Dose which reduces the ulcer index in the treated group by 50% in comparison with the control group

LD_{50} = Dose at which 50% of the animals die

TQ = Therapeutic quotient LD_{50}/ED_{50}

+) % inhibition = inhibition of gastric secretion (in %) 4 hours after administration of the anti-ulcerogenic ED_{50}

It should be pointed out in particular that although an ED_{50} can still be detected for compound 1, the dose/effect curve has then become very considerably flatter, so that even at 300 mg/kg no substantial increase in the anti-ulcerogenic action can be achieved. In contrast, the action of compounds 2 to 5 is strictly dose-dependent; inhibiting effects of up to 95% can be achieved.

The anti-ulcerogenic action was tested by the method of the so-called Shay rat:

Ulcers are provoked in rats which have been fasted for 24 hours (female, 180-200 g, 4 animals per cage on a high grating), by pylorus ligature (under diethyl ether anaesthesia) and oral administration of 100 mg/10 ml/kg of acetylsalicylic acid. The substances to be tested are administered orally (10 ml/kg) 1 hour before the pylorus ligature. The wound is closed by means of Michel clamps. 4 hours thereafter, the animals are sacrificed under ether anaesthesia by atlas dislocation and the stomach is resected. The stomach is opened longitudinally and fixed on a cork plate, after the amount of gastric juice secreted (volume) has been determined; the number and size (= diameter) of the ulcers present are determined with a stereomicroscope under 10-fold magnification. The product of the degree of severity (according to the following points scale) and the number of ulcers serves as the individual ulcer index.

Points scale:

No ulcers 0
Ulcer diameter 0.1-1.4 mm 1
1.5-2.4 mm 2
2.5-3.4 mm 3
3.5-4.4 mm 4
4.5-5.4 mm 5
> 5.5 mm 6

The reduction in the average ulcer index of each group treated in comparison with that of the control group (= 100%) serves as a measure of the anti-ulcerogenic effect. The ED_{50} designates the dose which reduces the average ulcer index by 50%.

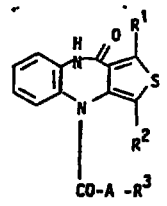
Determination of the toxicity

The toxicity studies were carried out on female NMRI mice (body weight 22-26 g). The animalS (5 animals per dose) received food and water ad libitum. Various doses of the substances are administered intravenously (injection time 1 minute). The observation period is 7 days. The LD_{50}, that is to say the dose at which 50% of the animals die, is determined by means of linear regression.

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Claims (for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

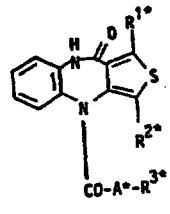
1. Substituted thienobenzodiazepinones of the general formula I



(I)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^3 denotes a halogen atom or the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R^7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and their acid addition salts.

2. Substituted thienobenzodiazepinones according to Claim 1, characterized by the general formula I*



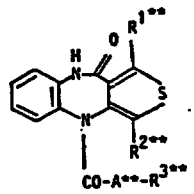
(I*)

wherein R^{1*} denotes a hydrogen atom or a methyl or ethyl radical, R^{2*} represents a chlorine atom or has one of the

* C L M S *

meanings of R^{1*}, R^{3*} denotes a chlorine atom and A* denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms.

3. Substituted thienobenzodiazepinones according to Claim 1, characterized by the general formula I**



(I**)

wherein R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}, R^{3**} denotes the group $-N(R^{4**})R^{5**}$ and R^{4**} denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 4 carbon atoms and R^{5**} has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}-N(R^{6**})R^{7**}$, or R^{4**} and R^{5**}, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^{6**} denotes a methyl or ethyl group, R^{7**} denotes a methyl or ethyl group, m** denotes 2 or 3 and A** denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, and their acid addition salts.

4. Compounds according to Claim 3, in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} denotes a methyl or ethyl radical and R^{5**} has the meaning of R^{4**} or represents the group $(CH_2)_{m**}-N(R^{6**})R^{7**}$ or R^{4**} and R^{5**}, together and including the nitrogen atom, denote a pyrrolidino, piperidino or hexahydroazepin-1-yl radical, and R^{6**} and R^{7**} denote a methyl or ethyl

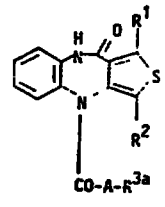
* C L M S *

radical, m** denotes 2 and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts.

5. Compounds according to Claim 3, in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts.

6. Compounds according to Claim 3, in which R^{1**} denotes a hydrogen atom or a methyl radical, R^{2**} denotes a hydrogen atom or a methyl radical, R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts.

7, Medicaments which contain one or more thienobenzodiazepinones of the general formula Ia



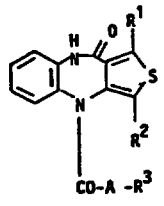
(Ia)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^{3a} denotes the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl

* C L M S *

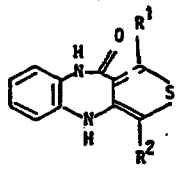
group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazione-1-yl group or a hexahydro-III-1,4-diazepin-1-yl group which is substituted in the 4 position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and/or their pharmacologically acceptable acid addition salts.

8. Process for the preparation of the substituted thienobenzodiazepinones of the general formula I



(I)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^3 denotes a halogen atom or the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R^7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and their acid addition salts, characterized in that thienobenzodiazepinones of the general formula II



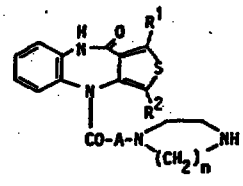
(II)

wherein R^1 and R^2 have the abovementioned meaning, are acylated and, if appropriate, the products are then aminated and/or bases obtained are converted into acid addition salts or acid addition salts obtained are converted into the free base or pharmacologically acceptable acid addition salts.

9. Process according to Claim 8, characterized in that the acylation is carried out with compounds of the general formulae Hal-A-CO-Hal' (III) or $(Hal\text{-}A\text{-}CO)_2O$ (IV), wherein Hal and Hal' denote a halogen atom and A denotes an alkylene group with 1 to 5 carbon atoms.

10. Process according to Claim 8, characterized in that compounds of the general formula I wherein R^3 represents a halogen atom and secondary amines of the general formula $HN(R^4)R^5$ (V), wherein R^4 and R^5 have the meaning given in Claim 8, are employed in the amination to be carried out subsequently, if appropriate.

11. Process according to Claim 10, characterized in that piperazine or homopiperazine is employed as the secondary amine V in the amination to be carried out subsequently, if appropriate, and the resulting reaction product of the general formula X



(X)

wherein R^1, R^2 and A have the meaning given in Claim 8, and n denotes 2 or 3, is methylated or ethylated.

12. Process according to Claim 8, characterized in that the acylation is carried out with compounds of the

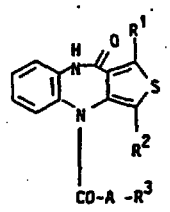
general formula Z-CO-A-N(R^4)R^5 (IX), wherein A, R^4 and R^5 have the meanings given in Claim 8 and Z represents a detachable group.

13. Substituted thienobenzodiazepinones of the general formula Ia, wherein the substituents have the meaning given in Claim 7, for use in the treatment and prophylaxis of illnesses based on diseases of the stomach or intestine.

14. Compound according to Claim 3, in which R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group, and its pharmacologically acceptable acid addition salts.

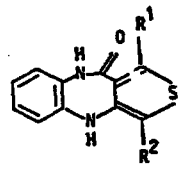
Claims (for the contracting state AT)

1. Process for the preparation of substituted thienobenzodiazepinones of the general formula I



(I)

wherein R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, R^2 represents a halogen atom or has one of the meanings of R^1, R^3 denotes a halogen atom or the group $-N(R^4)R^5$ and R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or R^4 and R^5, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^6 denotes an alkyl group with 1 to 4 carbon atoms, R^7 denotes an alkyl group with 1 to 4 carbon atoms, A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and m denotes 2 or 3, and their acid addition salts, characterized in that thienobenzodiazepinones of the general formula II



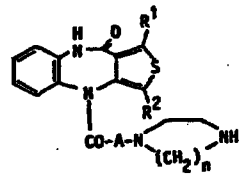
(II)

wherein R^1 and R^2 have the abovementioned meaning, are acylated and, if appropriate, the products are then aminated and/or bases obtained are converted into acid addition salts or acid addition salts obtained are converted into the free base or pharmacologically acceptable acid addition salts.

2. Process according to Claim 1, characterized in that the acylation is carried out with compounds of the general formulae Hal-A-CO-Hal' (III) or $(Hal-A-CO)_2O$ (IV), wherein Hal and Hal' denote a halogen atom and A denotes an alkylene group with 1 to 5 carbon atoms.

3. Process according to Claim 1, characterized in that compounds of the general formula I wherein R^3 represents a halogen atom and secondary amines of the general formula $HN(R^4)R^5$ (V), wherein R^4 and R^5 have the meaning given in Claim 3, are employed in the amination to be carried out subsequently, if appropriate.

4. Process according to Claim 3, characterized in that piperazine or homopiperazine is employed as the secondary amine V in the amination to be carried out subsequently, if appropriate, and the resulting reaction product of the general formula X

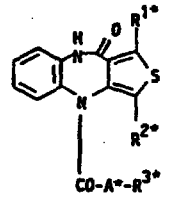


(X)

wherein R^1, R^2 and A have the meaning given in Claim 1, and n denotes 2 or 3, is methylated or ethylated.

5. Process according to Claim 1, characterized in that the acylation is carried out with compounds of the detachable general formula $Z-CO-A-N(R^4)R^5$ (IX), wherein A, R^4 and R^5 have the meanings given in Claim 1 and Z represents a group.

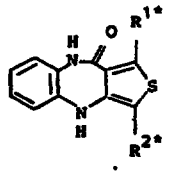
6. Process according to Claim 1 and 2, characterized in that substituted thienobenzodiazepinones of the general formula I*



(I*)

wherein R^{1*} denotes a hydrogen atom or a methyl or ethyl

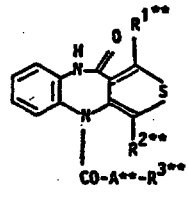
radical, R^{2*} represents a chlorine atom or has one of the meanings of R^{1*}, R^{3*} denotes a chlorine atom and A* denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, are prepared by reacting thienobenzodiazepinones of the general formula II*



(II*)

wherein R^{1*} and R^{2*} have the abovementioned meaning, with acid derivatives III* Cl-A*-CO-Cl (III*) or IV* $(Cl\text{-}A^*\text{-}CO)_2O$ (IV*), wherein A* has the abovementioned meaning.

7. Process according to Claim 1 and 3, characterized in that substituted thienobenzodiazepinones of the general formula I**



(I**)

wherein R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}, R^{3**} denotes the group $-N(R^{4**})R^{5**}$ and R^{4**} denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 4 carbon atoms and R^{5**} has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}-N(R^{6**})R^{7**}$, or R^{4**} and R^{5**}, together and including the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, and R^{6**} denotes a methyl or ethyl group, R^{7**} denotes a methyl or ethyl group, m** denotes 2 or 3

and A** denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, and their acid addition salts, are prepared by reaction of compounds of the general formula I**, wherein R^{3**} denotes a chlorine atom, with amines of the general formula V** $HN(R^{4**})R^{5**}$ (V**), wherein R^{4**} and R^{5**} have the abovementioned meaning.

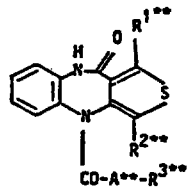
8. Process according to Claim 7, characterized in that compounds of the general formula I** in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} denotes a methyl or ethyl radical and R^{5**} has the meaning of R^{4**} or represents the group $(CH_2)_{m**}-N(R^{6**})R^{7**}$ or R^{4**} and R^{5**}, together and including the nitrogen atom, denote a pyrrolidino, piperidino or hexahydroazepin-1-yl radical, and R^{6**} and R^{7**} denote a methyl or ethyl radical, m** denotes 2 and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts, are prepared.

9. Process according to Claim 7, characterized in that compounds of the general formula I** in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts are prepared.

10. Process according to Claim 7, characterized in that compounds of the general formula I** in which R^{1**} denotes a hydrogen atom or a methyl radical, R^{2**} denotes a hydrogen atom or a methyl radical, R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group

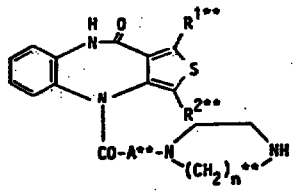
which is substituted in the 4-position by a methyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts are prepared.

11. Process according to Claim 1 and 4, characterized in that substituted thienobenzodiazepinones of the general formula I**



(I**)

wherein R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom to which they are bonded, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl or ethyl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group and A** denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, and their acid addition salts are prepared by reaction of compounds of the general formula I**, wherein R^{3**} denotes a chlorine atom, with piperazine or homopiperazine as amines of the general formula V** and methylation or ethylation of the resulting piperazinothienobenzodiazepinones of the general formula X**



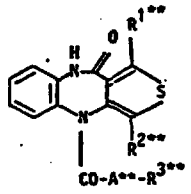
(X**)

wherein R^{1**}, R^{2**} and A** have the abovementioned meaning and n** denotes 2 or 3.

12. Process according to Claim 11, characterized in that compounds of the general formula I** in which R^{1**}

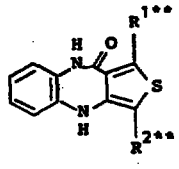
denotes a hydrogen atom or a methyl radical, R^{2**} has one of the meanings of R^{1**}; R^{3**} represents the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group, and their pharmacologically acceptable acid addition salts are prepared.

13. Process according to Claim 1 and 5, characterized in that substituted thienobenzodiazepinones of the general formula I**



(I**)

wherein R^{1**}, R^{2**}, R^{3**} and A** have the meaning given in Claim 7, are prepared by reaction of thienobenzodiazepinones of the general formula II**.



(II**)

wherein R^{1**} and R^{2**} have the abovementioned meaning, with reactive acid derivatives of the general formula IX** $Z^{**}-CO-A^{**}-N-(R^{4**})R^{5**}$ (IX**), wherein Z** represents a detachable group and A**, R^{4**} and R^{5**} have the meaning given in Claim 7.

14. Process according to Claim 7, characterized in that the compound of the general formula I** in which R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group and their pharmacologically acceptable acid addition salts are prepared.

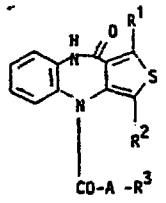
15. Process according to Claim 11, characterized in that the compound of the general formula I** in which R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group and their pharmacologically acceptable acid addition salts are prepared.

16. Process according to Claim 13, characterized in that the compound of the general formula I** in which R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**}, together and including the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A** denotes a methylene group and their pharmacologically acceptable acid addition salts are prepared.

* C L M S *

Ansprüche (für die Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. Substituierte Thienobenzodiazepinone der allgemeinen Formel I



(I)

worin

R^1 ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeutet,

R^2 ein Halogenatom darstellt oder eine der Bedeutungen von R^1 hat,

R^3 ein Halogenatom oder die Gruppe $-N(R^4)R^5$ und

R^4 einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder einen Alkenylrest mit 3 bis 5 Kohlenstoffatomen bedeuten,

R^5 eine der Bedeutungen von R^4 hat oder die Gruppe $-(CH_2)_m-N(R^6)R^7$ darstellt oder

R^4 und R^5 gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine Morpholinogruppe, eine Pyrrolidinogruppe, eine Piperidinogruppe, eine Hexahydroazepin-1-yl-gruppe, eine gegebenenfalls in 4-Position durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethylpiperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1H-1,4-diazepin-1-yl-gruppe bedeuten und

R^6 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen

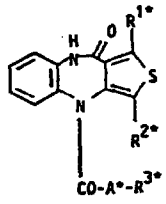
R^7 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

A eine geradkettige oder verzweigte Alkylengruppe mit 1 bis 5 Kohlenstoffatomen und

m 2 oder 3 bedeuten,

sowie ihre Säureadditionssalze.

2. Substituierte Thienobenzodiazepinone nach Anspruch 1, gekennzeichnet durch die allgemeine Formel I^*



(I^*)

worin

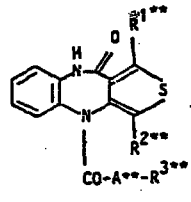
R^{1*} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet,

R^{2*} ein Chloratom darstellt oder eine der Bedeutungen von R^{1*} hat,

R^{3*} ein Chloratom und

A^* eine geradkettige oder verzweigte Alkylengruppe mit 1 oder 2 Kohlenstoffatomen bedeuten.

3. Substituierte Thienobenzodiazepinone nach Anspruch 1, gekennzeichnet durch die allgemeine Formel I^{**}



(I^{**})

worin

R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet,

R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat.

R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ und

R^{4**} einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen bedeuten,

R^{5**} die Bedeutung von R^{4**} hat oder die Gruppe $-(CH_2)_{m**}-N(R^{6**})R^{7**}$ darstellt oder

R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine Morpholinogruppe, eine Pyrrolidinogruppe, eine Piperidinogruppe, eine Hexahydroazepin-1-yl-gruppe, eine gegebenenfalls in 4-Position durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethyl-piperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1H-1,4-diazepin-1-yl-gruppe bedeuten und

R^{6**} eine Methyl- oder Ethylgruppe,

R^{7**} eine Methyl- oder Ethylgruppe,

m^{**} 2 oder 3,

A^{**} eine geradkettige oder verzweigte Alkylengruppe mit 1 oder 2 Kohlenstoffatomen bedeuten,

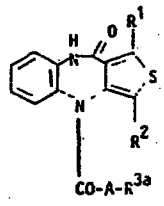
und ihre Säureadditionssalze.

4. Verbindungen nach Anspruch 3, in denen R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet, R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat; R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} einen Methyl- oder Ethylrest bedeutet, R^{5**} die Bedeutung von R^{4**} hat oder die Gruppe $(CH_2)_{m**}-N(R^{6**})R^{7**}$ darstellt oder R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms einen Pyrrolidino-, Piperidino- oder Hexahydroazepin-1-yl-rest, R^{6**} und R^{7**} einen Methyl- oder Ethylrest, m^{**} 2 und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze.

5. Verbindungen nach Anspruch 3, in denen R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet, R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat; R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethylpiperazin-1-yl-gruppe oder eine in 4-Stellung durch eine Methyl- oder Ethylgruppe substituierte hexahydro-1H-1,4-diazepin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze.

6. Verbindungen nach Anspruch 3, in denen R^{1**} ein Wasserstoffatom oder einen Methylrest, R^{2**} ein Wasserstoffatom oder einen Methylrest darstellt, R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze.

7. Arzneimittel, die ein oder mehrere Thienobenzodiazepinone der allgemeinen Formel Ia



(Ia)

worin

R^1 ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeutet,

R^2 ein Halogenatom darstellt oder eine der Bedeutungen von R^1 hat,

R^{3a} die Gruppe $-N(R^4)R^5$ und

R^4 einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder einen Alkenylrest mit 3 bis 5 Kohlenstoffatomen bedeuten,

R^5 eine der Bedeutungen von R^4 hat oder die Gruppe $-(CH_2)_m-N(R^6)R^7$ darstellt oder

R^4 und R^5 gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine Morpholinogruppe, eine Pyrrolidinogruppe, eine Piperidinogruppe, eine Hexahydroazepin-1-yl-gruppe, eine gegebenenfalls in 4-Position durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethylpiperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1H-1,4-diazepin-1-yl-gruppe bedeuten und

R^6 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

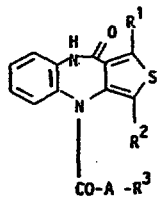
R^7 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

A eine geradkettige oder verzweigte Alkylengruppe mit 1 bis 5 Kohlenstoffatomen und

m 2 oder 3 bedeuten,

und/oder ihre pharmakologisch verträglichen Säureadditionssalze enthalten.

8. Verfahren zur Herstellung der substituierten Thienobenzodiazepinone der allgemeinen Formel I



(I)

worin

R^1 ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeutet,

R^2 ein Halogenatom darstellt oder eine der Bedeutungen von R^1 hat,

R^3 ein Halogenatom oder die Gruppe $-N(R^4)R^5$ und

R^4 einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder einen Alkenylrest mit 3 bis 5 Kohlenstoffatomen bedeuten,

R^5 eine der Bedeutungen von R^4 hat oder die Gruppe $-(CH_2)_m-N(R^6)R^7$ darstellt oder

R^4 und R^5 gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine Morpholinogruppe, eine Pyrrolidinogruppe, eine Piperidinogruppe, eine Hexahydroazepin-1-yl-gruppe, eine gegebenenfalls in 4-Position durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethylpiperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1H-1,4-diazepin-1-yl-gruppe bedeuten und

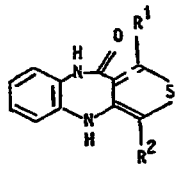
R^6 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

R^7 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

A eine geradkettige oder verzweigte Alkylengruppe mit 1 bis 5 Kohlenstoffatomen und

m 2 oder 3 bedeuten,

sowie ihrer Säureadditionssalze, dadurch gekennzeichnet, daß man Thienobenzodiazepinone der allgemeinen Formel II



(II)

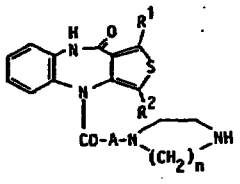
worin

R^1 und R^2 die oben angegebene Bedeutung haben, acyliert und gegebenenfalls anschließend aminiert und/oder erhaltenen Basen in die Säureadditionssalze oder erhaltene Säureadditionssalze in die freie Base oder pharmakologisch verträgliche Säureadditionssalze überführt.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man die Acylierung mit Verbindungen der allgemeinen Formeln Hal—A—CO—Hal' (III) oder $(Hal—A—CO)_2O$ (IV), worin Hal und Hal' ein Halogenatom und A eine Alkylengruppe mit 1 bis 5 Kohlenstoffatomen bedeuten, durchführt.

10. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man bei der sich gegebenenfalls anschließenden Aminierung Verbindungen der allgemeinen Formel I, worin R^3 ein Halogenatom darstellt, und sekundäre Amine der allgemeinen Formel $HN(R^4)R^5$ (V), worin R^4 und R^5 die in Anspruch 8 angegebene Bedeutung haben, einsetzt.

11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß man bei der sich gegebenenfalls anschließenden Aminierung als sekundäre Amine V Piperazin oder Homopiperazin einsetzt und das erhaltene Reaktionsprodukt der allgemeinen Formel X



(X)

worin R^1, R^2 und A die in Anspruch 8 angegebene Bedeutung haben und n 2 oder 3 bedeutet, methyliert oder ethyliert.

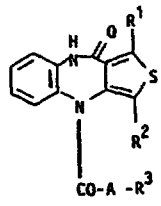
12. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man die Acylierung mit Verbindungen der allgemeinen Formel Z—CO—A—$N(R^4)R^5$ (IX), worin A, R^4 und R^5 die in Anspruch 8 angegebene Bedeutungen haben und Z eine Fluchtgruppe darstellt, durchführt.

13. Substituierte Thienobenzodiazepinone der allgemeinen Formel Ia, worin die Substituenten die in Anspruch 7 angegebene Bedeutung haben, zur Anwendung bei der Behandlung und Prophylaxe von Krankheiten, die auf Erkrankungen des Magens oder Darms beruhen.

14. Verbindung nach Anspruch 3, in der R^{1**} ein Wasserstoffatom, R^{2**} einen Methylrest, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze.

Ansprüche (für den Vertragsstaat AT)

1. Verfahren zur Herstellung von substituierten Thienobenzodiazepinonen der allgemeinen Formel I



(I)

worin

R^1 ein Wasserstoffatom oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeutet,

R^2 ein Halogenatom darstellt oder eine der Bedeutungen von R^4 hat,

R^3 ein Halogenatom oder die Gruppe —$N(R^4)R^5$ und

R^4 einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder einen Alkenylrest mit 3 bis 5 Kohlenstoffatomen bedeuten,

R^5 eine der Bedeutungen von R^4 hat oder die Gruppe —$(CH_2)_m$—$N(R^6)R^7$ darstellt oder

R^4 und R^5 gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine Morpholinogruppe, eine Pyrrolidinogruppe, eine Piperidinogruppe, eine Hexahydroazepin-1-yl-gruppe, eine gegebenenfalls in 4-Position durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethylpiperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1 H-1,4-diazepin-1-yl-gruppe bedeuten und

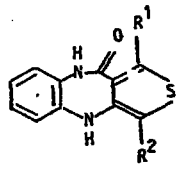
R^6 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

R^7 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

A eine geradkettige oder verzweigte Alkylengruppe mit 1 bis 5 Kohlenstoffatomen und

m 2 oder 3 bedeuten,

sowie ihren Säureadditionssalzen, dadurch gekennzeichnet, daß man Thienobenzodiazepinone der allgemeinen Formel II



(II)

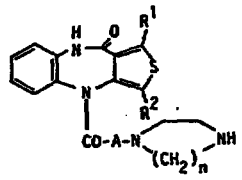
worin R^1 und R^2 die oben angegebene Bedeutung haben, acyliert und gegebenenfalls anschließend aminiert und/oder erhaltene Basen in die Säureadditionssalze oder erhaltene Säureadditionssalze in die freie Base oder pharmakologisch vertragliche Säureadditionssalze überführt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man die Acylierung mit Verbindungen der allgemeinen Formeln Hal—A—CO—Hal' (III) oder $(Hal—A—CO)_2O$ (IV), worin Hal und Hal' ein Halogenatom und A eine Alkylengruppe mit 1 bis 5 Kohlenstoffatomen bedeuten, durchführt.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man bei der sich gegebenenfalls anschließenden Aminierung Verbindungen der allgemeinen Formel I, worin R^2 ein Halogenatom darstellt,

und sekundäre Amine der allgemeinen Formel $HN(R^4)R^5$ (V), worin R^4 und R^5 die in Anspruch 1 angegebene Bedeutung haben, einsetzt.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man bei der sich gegebenenfalls anschließenden Aminierung als sekundäre Amine V Piperazin oder Homopiperazin einsetzt und das erhaltene Reaktionsprodukt der allgemeinen Formel X

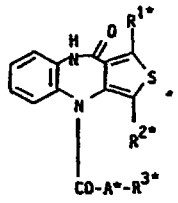


(X)

worin R^1, R^2 und A die in Anspruch 1 angegebene Bedeutung haben und n 2 oder 3 bedeutet, methyliert oder ethyliert.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man die Acylierung mit Verbindungen der allgemeinen Formel $Z—CO—A—N(R^4)R^5$ (IX), worin A, R^4 und R^5 die in Anspruch 1 angegebenen Bedeutungen haben und Z eine Fluchtgruppe darstellt, durchführt.

6. Verfahren nach Anspruch 1 und 2, dadurch gekennzeichnet, daß man substituierte Thienobenzodiazepinone der allgemeinen Formel I*



(I*)

worin

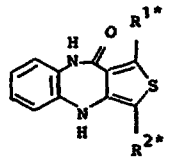
R^{1*} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet,

R^{2*} ein Chloratom darstellt oder eine der Bedeutungen von R^{1*} hat,

R^{3*} ein Chloratom und

A^* eine geradkettige oder verzweigte Alkylengruppe mit 1 oder 2 Kohlenstoffatomen bedeuten,

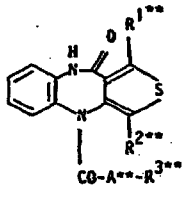
durch Umsetzung von Thienobenzodiazepinonen der allgemeinen Formel II*



(II*)

worin R^{1*} und R^{2*} die oben angegebene Bedeutung haben, mit Säurederivaten III* Cl—A*—CO—Cl (III*) oder IV* $(Cl—A^*—CO)_2O$ (IV*), worin A* die oben angegebene Bedeutung hat, herstellt.

7. Verfahren nach Anspruch 1 und 3, dadurch gekennzeichnet, daß man substituierte Thienobenzodiazepinone der allgemeinen Formel I**



(I**)

worin

R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet,

R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat,

R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ und

R^{4**} einen Alkylrest mit 1 bis 4 Kohlenstoffatomen oder einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen bedeuten,

R^{5**} die Bedeutung von R^{4**} hat oder die Gruppe $-(CH_2)_{m**}-N(R^{6**})R^{7**}$ darstellt oder

R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine Morpholinogruppe, eine Pyrrolidinogruppe, eine Piperidinogruppe, eine Hexahydroazepin-1-yl-gruppe, eine gegebenenfalls in 4-Position durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethyl-piperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1H-1,4-diazepin-1-yl-gruppe bedeuten und

R^{6**} eine Methyl- oder Ethylgruppe,

R^{7**} eine Methyl- oder Ethylgruppe,

m^{**} 2 oder 3,

A^{**} eine geradkettige oder verzweigte Alkylengruppe mit 1 oder 2 Kohlenstoffatomen bedeuten,

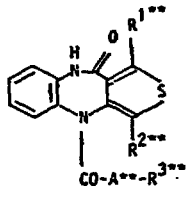
und ihre Säureadditionssalze durch Umsetzung von Verbindungen der allgemeinen Formel I^{**}, worin R^{3**} ein Chloratom bedeutet, mit Aminen der allgemeinen Formel V^{**} $HN(R^{4**})$ R^{5**} (V^{**}), worin R^{4**} und R^{5**} die oben angegebene Bedeutung haben, herstellt.

8. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man Verbindungen der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet, R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat; R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} einen Methyl- oder Ethylrest bedeutet, R^{5**} die Bedeutung von R^{4**} hat oder die Gruppe $-(CH_2)_{m**}-N(R^{6**})R^{7**}$ darstellt oder R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms einen Pyrrolidino-, Piperidino- oder Hexahydroazepin-1-yl-rest, R^{6**} und R^{7**} einen Methyl- oder Ethylrest, m^{**} 2 und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

9. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man Verbindungen der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet, R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat; R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine gegebenenfalls in 4-Stellung durch eine Methyl-, Ethyl- oder Benzylgruppe substituierte Piperazin-1-yl-gruppe, eine 2,4-Dimethyl-piperazin-1-yl-gruppe oder eine in 4-Stellung durch eine Methyl- oder Ethylgruppe substituierte hexahydro-1H-1,4-diazepin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

10. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man Verbindungen der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom oder einen Methylrest, R^{2**} ein Wasserstoffatom oder einen Methylrest bedeutet, R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

11. Verfahren nach Anspruch 1 und 4, dadurch gekennzeichnet, daß man substituierte Thienobenzodiazepinone der allgemeinen Formel I^{**}



(I^{**})

worin

R^{1**} ein Wasserstoffatom, einen Methyl- oder Ethylrest bedeutet,

R^{2**} ein Chloratom darstellt oder eine der Bedeutungen von R^{1**} hat,

R^{3**} die Gruppe $-N(R^{4**})R^{5**}$,

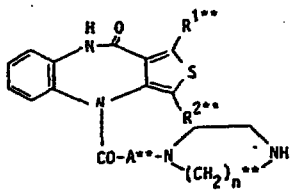
R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms, an das sie gebunden sind, eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Piperazin-1-yl-gruppe oder eine in 4-Position durch eine Methyl- oder Ethylgruppe substituierte Hexahydro-1H-1,4-diazepin-1-yl-gruppe bedeuten,

A^{**} eine geradkettige oder verzweigte Alkylengruppe mit 1 oder 2 Kohlenstoffatomen bedeuten,

und ihre Säureadditionssalze durch Umsetzung von Verbindungen der allgemeinen Formel I^{**}, worin

* C L M S *

R^{3**} ein Chloratom bedeutet, mit Piperazin oder Homopiperazin als Aminen der allgemeinen Formel V^{**} und Methylierung oder Ethylierung der erhaltenen Piperazinothienobenzodiazepinone der allgemeinen Formel X^{**}

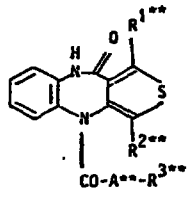


(X^{**})

worin R^{1**}, R^{2**} und A^{**} die vorstehend angegebene Bedeutung haben und n^{**} 2 oder 3 bedeutet, herstellt.

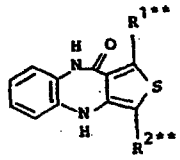
12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß man Verbindungen der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom oder einen Methylrest bedeutet, R^{2**} eine der Bedeutungen von R^{1**} hat; R^{3**} die Gruppe $-N(R^{4**})R^{5**}$ darstellt, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

13. Verfahren nach Anspruch 1 und 5, dadurch gekennzeichnet, daß man substituierte Thienobenzodiazepinone der allgemeinen Formel I^{**}



(I^{**})

worin R^{1**}, R^{2**}, R^{3**} und A^{**} die in Anspruch 7 angegebene Bedeutung haben, durch Umsetzung von Thienobenzodiazepinonen der allgemeinen Formel II^{**}



(II^{**})

worin R^{1**} und R^{2**} die vorstehend angegebene Bedeutung haben, mit reaktiven Säurederivaten der allgemeinen Formel IX^{**} $Z^{**}—CO—A^{**}—N—(R^{4**})R^{5**}$ (IX^{**}), worin Z^{**} eine Fluchtgruppe darstellt und A^{**}, R^{4**} und R^{5**} die in Anspruch 7 angegebene Bedeutung haben, herstellt.

14. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man die Verbindung der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom, R^{2**} einen Methylrest, R^{3**} die Gruppe $-N(R^{4**})R^{5**}$, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

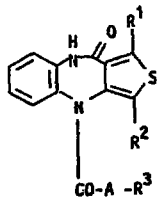
15. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß man die Verbindung der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom, R^{2**} einen Methylrest, R^{3**} die Gruppe $-N(R^{4**})R^{5**}$, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

16. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß man die Verbindung der allgemeinen Formel I^{**}, in der R^{1**} ein Wasserstoffatom, R^{2**} einen Methylrest, R^{3**} die Gruppe $-N(R^{4**})R^{5**}$, R^{4**} und R^{5**} gemeinsam unter Einschluß des Stickstoffatoms eine in 4-Stellung durch eine Methylgruppe substituierte Piperazin-1-yl-gruppe und A^{**} eine Methylengruppe bedeuten, sowie ihre pharmakologisch verträglichen Säureadditionssalze herstellt.

* C L M S *

Claims (for the contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE) (as published)

1. Substituted thienobenzodiazepinones of the general formula I

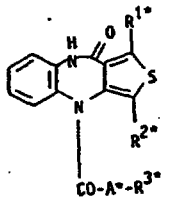


(I)

wherein

R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms,
R^2 represents a halogen atom or has one of the meanings of R^1,
R^3 denotes a halogen atom or the group $-N(R^4)R^5$,
R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms,
R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or
R^4 and R^5 together, and with the inclusion of the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,
R^6 denotes an alkyl group with 1 to 4 carbon atoms,
R^7 denotes an alkyl group with 1 to 4 carbon atoms,
A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and
m denotes 2 or 3,
and their acid addition salts.

2. Substituted thienobenzodiazepinones according to Claim 1, characterised by the general formula I*

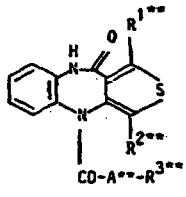


(I*)

wherein

R^{1*} denotes a hydrogen atom or a methyl or ethyl radical,
R^{2*} represents a chlorine atom or has one of the meanings of R^{1*},
R^{3*} denotes a chlorine atom and
A^* denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms.

3. Substituted thienobenzodiazepinones according to Claim 1, characterised by the general formula I**



(I**)

wherein

R^{1**} denotes a hydrogen atom or a methyl or ethyl radical,

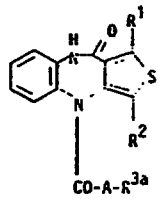
R^{2**} represents a chlorine atom or has one of the meanings of R^{1**},
R^{3**} denotes the group $-N(R^{4**})R^{5**}$,
R^{4**} denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 4 carbon atoms,
R^{5**} has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}-N(R^{6**})R^{7**}$, or
R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,
R^{6**} denotes a methyl or ethyl group,
R^{7**} denotes a methyl or ethyl group,
m^{**} denotes 2 or 3 and
A^{**} denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms,
and their acid addition salts.

4. Compounds according to Claim 3, in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} denotes the group $-N(R^{4**})R^{5**}$; R^{4**} denotes a methyl or ethyl radical and R^{5**} has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}-N(R^{6**})R^{7**}$, or R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a pyrrolidino, piperidino or hexahydroazepin-1-yl radical, R^{6**} and R^{7**} denote a methyl or ethyl radical, m^{**} denotes 2 and A^{**} denotes a methylene group, and their pharmacologically acceptable acid addition salts.

5. Compounds according to Claim 3, in which R^{1**} denotes a hydrogen atom or a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group; and A^{**} denotes a methylene group, and their pharmacologically acceptable acid addition salts.

6. Compounds according to Claim 3, in which R^{1**} denotes a hydrogen atom or a methyl radical, R^{2**} denotes a hydrogen atom or a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**} together, with inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methylene group and A^{**} denotes a methylene group, and their pharmacologically acceptable acid addition salts.

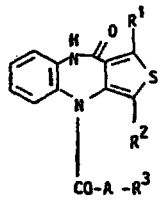
7. Medicaments containing one or more thienobenzodiazepinones of the general formula Ia



(Ia)

wherein
R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms,
R^2 represents a halogen atom or has one of the meanings of R^1,
R^{3a} denotes the group $-N(R^4)R^5$,
R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms and
R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or
R^4 and R^5 together, and with the inclusion of the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,
R^6 denotes an alkyl group with 1 to 4 carbon atoms,
R^7 denotes an alkyl group with 1 to 4 carbon atoms,
A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and
m denotes 2 or 3,
and/or their pharmacologically acceptable acid addition salts.

8. Process for the preparation of the substituted thienobenzodiazepinones of the general formula I



(I)

wherein

R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms,

R^2 represents a halogen atom or has one of the meanings of R^1,

R^3 denotes a halogen atom or the group $-N(R^4)R^5$,

R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms,

R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or

R^4 and R^5 together, and with the inclusion of the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,

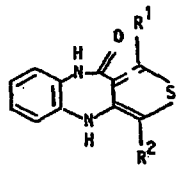
R^6 denotes an alkyl group with 1 to 4 carbon atoms,

R^7 denotes an alkyl group with 1 to 4 carbon atoms,

A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and

m denotes 2 or 3,

and their acid addition salts, characterised in that thienobenzodiazepinones of the general formula II



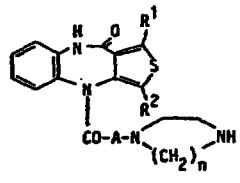
(II)

wherein R^1 and R^2 have the abovementioned meanings, are acylated and, if appropriate, are then aminated, and/or resulting bases are converted into the free base or into pharmacologically acceptable acid addition salts.

9. Process according to Claim 8, characterised in that the acylation is carried out with compounds of the general formulae Hal—A—CO—Hal (III) or $(Hal—A—CO)_2O$ (IV), wherein Hal and Hal' denote a halogen atom and A denotes an alkylene group with 1 to 5 carbon atoms.

10. Process according to Claim 8, characterised in that compounds of the general formula I wherein R^3 represents a halogen atom, and secondary amines of the general formula $HN(R^4)R^5$ (V), wherein R^4 and R^5 have the meaning given in Claim 8, are employed in the optional subsequent amination.

11. Process according to Claim 10, characterised in that piperazine or homopiperazine are employed as secondary amines V in the optional subsequent amination, and the obtained product of the general formula X



(X)

wherein R^1, R^2 and A have the meanings given in Claim 8 and n denotes 2 or 3, is methylated or ethylated.

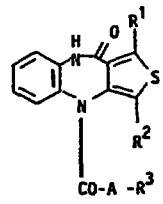
12. Process according to Claim 8, characterised in that the acylation is carried out with compounds of the general formula Z—CO—A—$N(R^4)R^5$ (IX), wherein Z denotes a leaving group and A, R^4 and R^5 have the meanings given in Claim 8.

13. Substituted thienobenzodiazepinones of the general formula Ia, wherein the substituents have the meanings given in Claim 7, for use in the treatment and prophylaxis of illnesses based on disorders of the stomach or intestine.

14. Compound according to Claim 3, in which R^{1**} denotes a hydrogen atom; R^{2**} denotes a methyl radical; R^{4**} and R^{5**}, and with the inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group; and A denotes a methylene group, and their pharmacologically acceptable acid addition salts.

Claims (for the Contracting State AT) (as published)

1. Process for the preparation of the substituted thieno-benzodiazepinones of the general formula I



(I)

wherein

R^1 denotes a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms,

R^2 represents a halogen atom or has one of the meanings of R^1,

R^3 denotes a halogen atom or the group $-N(R^4)R^5$,

R^4 denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 5 carbon atoms,

R^5 has one of the meanings of R^4 or represents the group $-(CH_2)_m-N(R^6)R^7$, or

R^4 and R^5 together, and with the inclusion of the nitrogen atom to which they are bonded, denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethyl-piperazin-1-yl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,

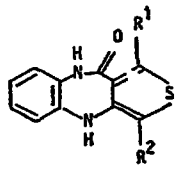
R^6 denotes an alkyl group with 1 to 4 carbon atoms,

R^7 denotes an alkyl group with 1 to 4 carbon atoms,

A denotes a straight-chain or branched alkylene group with 1 to 5 carbon atoms and

m denotes 2 or 3,

and their acid addition salts, characterised in that thienobenzodiazepinones of the general formula II



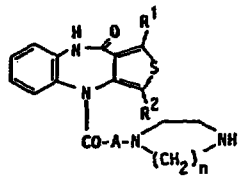
(II)

wherein R^1 and R^2 have the abovementioned meanings, are acylated and, if appropriate, are then aminated, and/or resulting bases are converted into the free base or into pharmacologically acceptable acid addition salts.

2. Process according to Claim 1, characterised in that the acylation is carried out with compounds of the general formulae Hal—A—CO—Hal' (III) or $(Hal—A—CO)_2O$ (IV), wherein Hal and Hal' denote a halogen atom and A denotes an alkylene group with 1 to 5 carbon atoms.

3. Process according to Claim 1, characterised in that compounds of the general formula I wherein R^3 represents a halogen atom, and secondary amines of the general formula $HN(R^4)R^5$ (V), wherein R^4 and R^5 have the meanings given in Claim 1, are employed in the optional subsequent amination.

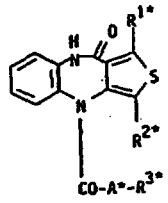
4. Process according to Claim 3, characterised in that piperazine or homopiperazine are employed as secondary amines V in the optional subsequent amination, and the obtained product of the general formula X



wherein R^1, R^2 and A have the meanings given in Claim 1 and n denotes 2 or 3, is methylated or ethylated.

5. Process according to Claim 1, characterised in that the acylation is carried out with compounds of the general formula Z—CO—A—N(R^4)R^5 (IX), wherein Z denotes a leaving group and A, R^4 and R^5 have the meanings given in Claim 1.

6. Process according to Claims 1 and 2, characterised in that substituted thienobenzodiazepinones of the general formula I*



(I*)

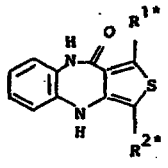
wherein

R^{1*} denotes a hydrogen atom, a methyl or ethyl radical,

R^{2*} denotes a chlorine atom or has one of the meanings of R^{1*},

R^{3*} denotes a chlorine atom,

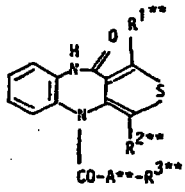
A^* denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms, are prepared by reaction of thienobenzodiazepinones of the general formula II*



(II*)

wherein R^{1*} and R^{2*} have the abovementioned meanings, with acid derivatives III* Cl—A^*—CO—Cl (III*) or IV* (Cl—A^*—CO)$_2$O (IV*), wherein A^* has the above mentioned meaning.

7. Process according to Claims 1 and 3, characterised in that substituted thienobenzodiazepinones of the general formula I**



(I**)

wherein

R^{1**} denotes a hydrogen atom, a methyl or ethyl radical,

R^{2**} denotes a chlorine atom or has one of the meanings or R^{1**},

R^{3**} denotes the group —N(R^{4**})R^{5**},

R^{4**} denotes an alkyl radical with 1 to 4 carbon atoms or an alkenyl radical with 3 to 4 carbon atoms,

R^{5**} has the meaning of R^{4**} or represents the group —$(CH_2)_m$—N(R^{6**})R^{7**}, or

R^{4**} and R^{5**} together, and with the inclusion of the nitrogen atom to which they are bonded,

denote a morpholino group, a pyrrolidino group, a piperidino group, a hexahydroazepin-1-yl group, a piperazin-1-yl group which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, 1 2,4-dimethyl-piperazin-1-yl group, a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,

R^{6**} denotes a methyl or ethyl group,

R^{7**} denotes a methyl or ethyl group,

m^{**} denotes 2 or 3 and

A^{**} denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms

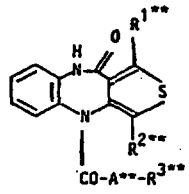
and their acid addition salts are prepared by reaction of compounds of the general formula I^{**}, wherein R^{3**} denotes a chlorine atom, with amines of the general formula V^{**} $HN(R^{4**})R^{5**}$ (V^{**}), wherein R^{4**} and R^{5**} have the abovementioned meanings.

8. Process according to Claim 7, characterised in that compounds of the general formula I^{**}, in which R^{1**} denotes a hydrogen atom, a methyl or ethyl radical, R^{2*} represents a chlorine atom or has one of the meanings of R^{1**}; R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} denotes a methyl or ethyl radical, R^{5**} has the meaning of R^{4**} or represents the group $-(CH_2)_{m**}-N(R^{6**})R^{7**}$, or R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a pyrrolidino, piperidino or hexahydroazepin-1-yl radical, R^{6**} and R^{7**} denote a methyl or ethyl radical, m^{**} denotes 2 and A^{**} denotes a methylene group, and their parmacologically acceptable acid addition salts are prepared.

9. Process according to Claim 7, characterised in that compounds of the general formula I^{**}, in which R^{1**} denotes a hydrogen atom, a methyl or ethyl radical, R^{2**} represents a chlorine atom or has one of the meanings of R^{1**}, R^{3**} denotes the group $-N(R^{4**})R^{5**}$; R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a piperazin-1-yl which is optionally substituted in the 4-position by a methyl, ethyl or benzyl group, a 2,4-dimethylpiperazin-1-yl group or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group and A^{**} denotes a methylene group, and their pharmacologically acceptable acid addition salts are prepared.

10. Process according to Claim 7, characterised in that compounds of the general formula I^{**}, in which R^{1**} denotes a hydrogen atom or a methyl radical, R^{2**} denotes a hydrogen atom or a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**} together, with inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group and A^{**} denotes a methylene group, and their pharmacologically acceptable acid addition salts are prepared.

11. Process according to Claims 1 and 4, characterised in that substituted thienobenzodiazepinones of the general formula I^{**}



(I^{**})

wherein

R^{1**} denotes a hydrogen atom, a methyl or ethyl radical,

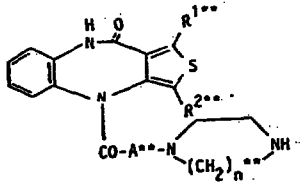
R^{2**} represents a chlorine atom or has one of the meanings of R^{1**},

R^{3**} denotes the group $-N(R^{4**})R^{5**}$,

R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom to which they are bonded, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl or ethyl group, or a hexahydro-1H-1,4-diazepin-1-yl group which is substituted in the 4-position by a methyl or ethyl group,

A^{**} denotes a straight-chain or branched alkylene group with 1 or 2 carbon atoms,

and their addition salts are prepared by reaction of compounds of the general formula I^{**}, wherein R^{3**} denotes a chlorine atom, with piperazine or homopiperazine as amines of the general formula V^{**} $HN(R^{4**})R^{5**}$ (V^{**}) and methylation or ethylation of the obtained piperazinothienobenzodiazepinones of the general formula X^{**}



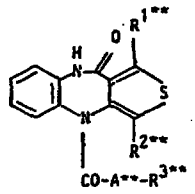
(X^{**})

* C L M S *

wherein R^{1**}, R^{2**} and A^{**} have the abovementioned meanings and n^{**} denotes 2 or 3.

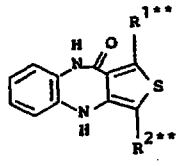
12. Process according to Claim 11, characterised in that compounds of the general formula I^{**}, wherein R^{1**} denotes a hydrogen atom or a methyl radical, R^{2**} has one of the meanings of R^{1**}, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group, A^{**} denotes a methylene group, and their pharmacologically acceptable acid addition salts are prepared.

13. Process according to Claims 1 and 5, characterised in that substituted thienobenzodiazepinones of the general formula I^{**}



(I^{**})

wherein R^{1**}, R^{2**}, R^{3**} and A^{**} have the meanings given in Claim 7, are prepared by reaction of thienobenzodiazepinones of the general formula II^{**}



(II^{**})

wherein R^{1**} and R^{2**} have the abovementioned meanings, with reactive acid derivatives of the general formula IX^{**} $Z^{**}-CO-A^{**}-N(R^{4**})R^{5**}$ (IX^{**}), wherein Z^{**} denotes a leaving group and A^{**}, R^{4**} and R^{5**} have the meanings given in Claim 7.

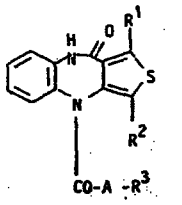
14. Process according to Claim 7, characterised in that the compound of the general formula I^{**}, wherein R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group, A^{**} denotes a methylene group, and its pharmacologically acceptable acid addition salts are prepared.

15. Process according to Claim 11, characterised in that the compound of the general formula I^{**}, wherein R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{3**} denotes the group $-N(R^{4**})R^{5**}$, R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group, A^{**} denotes a methylene group, and its pharmacologically acceptable acid addition salts are prepared.

16. Process according to Claim 13, characterised in that the compound of the general formula I^{*}, wherein R^{1**} denotes a hydrogen atom, R^{2**} denotes a methyl radical, R^{3**} denotes the group $-N(R^{4**}R^{5**})$, R^{4**} and R^{5**} together, with the inclusion of the nitrogen atom, denote a piperazin-1-yl group which is substituted in the 4-position by a methyl group, A^{**} denotes a methylene group, and its pharmacologically acceptable acid addition salts are prepared.

Revendications (pour les Etats contractants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. Thiénobenzodiazépinones substituées de la formule générale (I) (as published)



(I)

dans laquelle

R^1 représente un atome d'hydrogène ou un radical alkyle possédant de 1 à 4 atomes de carbone,

R^2 représente un atome d'halogène ou possède l'une des significations attribuées à R^1,

R^3 représente un atome d'halogène ou le radical $—N(R^4)R^5$ et

R^4 représente un radical alkyle possédant de 1 à 4 atomes de carbone ou un radical alcényle possédant de 3 à 5 atomes de carbone,

R^5 possède l'une des significations attribuées à R^4 ou représente un radical $—(CH_2)_m—N(R^6)R^7$, ou bien

R^4 et R^5 représentent en commun avec l'atome d'azote auquel ils sont attachés, un groupe morpholino, un groupe pyrrolidino, un groupe pipéridino, un groupe hexahydroazépin-1-yle, un groupe pipérazin-1-yle éventuellement substitué en position 4 par un radical méthyle, éthyle ou benzyle, un groupe 2,4-diméthylpipérazin-1-yle ou un groupe hexahydro-1H-1,4-diazépin-1-yle substitué en position 4 par un radical méthyle ou éthyle et

R^6 représente un groupe alkyle possédant de 1 à 4 atomes de carbone,

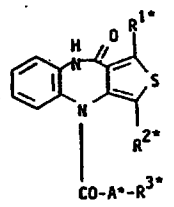
R^7 représente un groupe alkyle possédant de 1 à 4 atomes de carbone,

A représente un groupe alkylène à chaîne droite ou à chaîne ramifiée possédant de 1 à 5 atomes de carbone et

m est égal à 2 ou à 3,

comme aussi les sels d'addition d'acides de ces composés.

2. Thiénobenzodiazépinones substituées suivant la revendication 1, caractérisées en ce qu'ils répondent à la formule générale I*



(I*)

dans laquelle

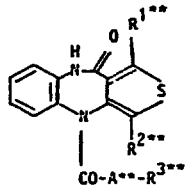
R^{1*} représente un atome d'hydrogène, un radical méthyle ou éthyle,

R^{2*} représente un atome de chlore ou possède l'une des significations attribuées à R^{1*},

R^{3*} représente un atome de chlore, et

A^* représente un groupe alkylène à chaîne droite ou à chaîne ramifiée possédant 1 ou 2 atomes de carbone.

3. Thiénobenzodiazépinones substituées suivant la revendication 1, caractérisées en ce qu'ils répondent à la formule générale I**



(I**)

dans laquelle

R^{1**} représente un atome d'hydrogène, un radical méthyle ou éthyle,

R^{2**} représente un atome de chlore ou possède l'une des significations attribuées à R^{1**},

R^{3**} représente le radical $—N(R^{4**})R^{5**}$ et

R^{4**} représente un radical alkyle possédant de 1 à 4 atomes de carbone ou un radical alcényle possédant 3 ou 4 atomes de carbone,

R^{5**} possède la signification attribuée à R^{4**} ou représente un groupe $—(CH_2)_m—N(R^{6**})R^{7**}$, ou bien

R^{4**} et R^{5**} représentent en commun avec l'atome d'azote auquel ils sont attachés, un groupe morpholino, un groupe pyrrolidino, un groupe pipéridino, un groupe hexahydroazépin-1-yle, un groupe pipérazin-1-yle éventuellement substitué en position 4 par un radical méthyle, éthyle ou benzyle, un groupe 2,4-diméthylpipérazin-1-yle ou un groupe hexahydro-1H-1,4-diazépin-1-yle substitué en position 4 par un radical méthyle ou éthyle et

R^{6**} représente un groupe méthyle ou éthyle,

R^{7**} représente un groupe méthyle ou éthyle.

m^{**} est égal à 2 ou à 3,

A^{**} représente un groupe alkylène à chaîne droite ou à chaîne ramifiée possédant 1 ou 2 atomes de carbone,

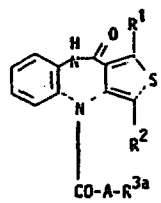
ainsi que les sels d'addition d'acides de ces composés.

4. Composés suivant la revendication 3, dans lesquels R^{1**} représente un atome d'hydrogène, le radical méthyle ou éthyle, R^{2**} représente un atome de chlore ou possède l'une des significations attribuées à R^{1**}, R^{3**} représente le groupe $-N(R^{4**})R^{5**}$, R^{4**} représente le radical méthyle ou éthyle, R^{5**} possède la signification attribuée à R^{4**} ou représente le groupe $(CH_2)_{m**}-N(R^{6**})R^{7**}$, ou bien R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un radical pyrrolidino, pipéridino ou hexahydroazépin-1-yle, R^{6**} et R^{7**} représente le radical méthyle ou éthyle, m^{**} est égal à 2 et A^{**} représente un radical méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.

5. Composés suivant la revendication 3, dans lesquels R^{1**} représente un atome d'hydrogène, le radical méthyle ou éthyle, R^{2**} représente un atome de chlore ou possède l'une des significations attribuées à R^{1**}, R^{3**} représente le groupe $-N(R^{4**})R^{5**}$, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un radical pipérazin-1-yle substitué en position 4 par un radical méthyle, éthyle ou benzyle, un radical 2,4-diméthylpipérazin-1-yle ou un radical hexahydro-1H-1,4-diazépin-1-yle substitué en position 4 par un radical méthyle ou éthyle et A^{**} représente un radical méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.

6. Composés suivant la revendication 3, dans lesquels R^{1**} représente un atome d'hydrogène ou le radical méthyle, R^{2**} représente un atome d'hydrogène ou un radical méthyle, R^{3**} représente le radical $-N(R^{4**})R^{5**}$, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un groupe pipérazin-1-yle substitué en position 4 par un radical méthyle et A^{**} représente un groupe méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.

7. Médicaments qui contiennent une ou plusieurs thiénobenzodiazépinones de la formule générale Ia



(Ia)

dans laquelle

R^1 représente un atome d'hydrogène ou un radical alkyle possédant de 1 à 4 atomes de carbone,

R^2 représente un atome d'halogène ou possède l'une des significations attribuées à R^1,

R^{3a} représente le groupe $-N(R^4)R^5$ et

R^4 représente un radical alkyle possédant de 1 à 4 atomes de carbone ou un reste alcénylе possédant de 3 à 5 atomes de carbone,

R^5 possède l'une des significations attribuées à R^4 ou représente le radical $-(CH_2)_m-N(R^6)R^7$, ou bien

R^4 et R^5 représentent en commun avec l'atome d'azote auquel ils sont attachés, un groupe morpholino, un groupe pyrrolidino, un groupe pipéridino, un groupe hexahydro-azépin-1-yle, un groupe pipérazin-1-yle éventuellement substitué en position 4 par un radical méthyle, éthyle, ou benzyle, un groupe 2,4-diméthyl-pipérazin-1-yle, ou un groupe hexahydro-1H-1,4-diazépin-1-yle substitué en position 4 par un groupe méthyle ou éthyle et

R^6 représente un radical alkyle possédant de 1 à 4 atomes de carbone,

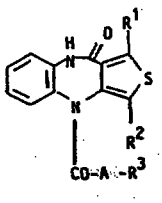
R^7 représente un radical alkyle possédant de 1 à 4 atomes de carbone,

A représente un radical alkylène à chaîne droite ou à chaîne ramifiée possédant de 1 à 5 atomes de carbone et

m est égal à 2 ou à 3,

et/ou leurs sels d'addition d'acides pharmacologiquement acceptables.

8. Procédé de préparation de thiénobenzodiazépinones substituées de la formule générale (I)



(I)

* C L M S *

dans laquelle

R^1 représente un atome d'hydrogène ou un radical alkyle possédant de 1 à 4 atomes de carbone,

R^2 représente un atome d'halogène ou possède l'une des significations attribuées à R^1,

R^3 représente un atome d'halogène ou le radical $-N(R^4)R^5$ et

R^4 représente un radical alkyle possédant de 1 à 4 atomes de carbone ou un radical alcényle possédant de 3 à 5 atomes de carbone,

R^5 possède l'une des significations attribuées à R^4 ou représente un radical $-(CH_2)_m-N(R^6)R^7$, ou bien

R^4 et R^5 représentent en commun avec l'atome d'azote auquel ils sont attachés, un groupe morpholino, un groupe pyrrolidino, un groupe pipéridino, un groupe hexahydroazépin-1-yle, un groupe pipérazin-1-yle éventuellement substitué en position 4 par un radical méthyle, éthyle ou benzyle, un groupe 2,4-diméthylpipérazin-1-yle ou un groupe hexahydro-1H-1,4-diazépin-1-yle substitué en position 4 par un radical méthyle ou éthyle et

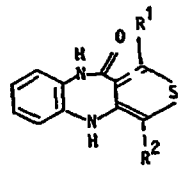
R^6 représente un groupe alkyle possédant de 1 à 4 atomes de carbone,

R^7 représente un groupe alkyle possédant de 1 à 4 atomes de carbone,

A représente un groupe alkylène à chaîne droite ou à chaîne ramifiée possédant de 1 à 5 atomes de carbone et

m est égal à 2 ou à 3,

comme aussi de leurs sels d'addition d'acides, caractérisé en ce que l'on procède à l'acylation de thiénobenzodiazépinones de la formule générale II



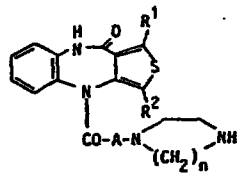
(II)

dans laquelle R^1 et R^2 possèdent les significations qui leur ont été attribuées plus haut et en ce qu'éventuellement l'on soumet les produits ainsi obtenus à une amination et/ou en ce que l'on convertit les bases obtenues en les sels d'addition d'acides ou en ce que l'on transforme les sels d'addition d'acides obtenus en les bases libres ou en les sels d'addition d'acides pharmacologiquement acceptables.

9. Procédé suivant la revendication 8, caractérisé en ce que l'on réalise l'acylation avec des composés de la formule générale Hal—A—CO—Hal' (III) ou $(Hal—A—CO)_2O$ (IV) dans laquelle Hal et Hal' représentent des atomes d'halogène et A représente un groupe alkylène possédant de 1 à 5 atomes de carbone.

10. Procédé suivant la revendication 8, caractérisé en ce qu'au cours de l'éventuelle amination subséquente, on utilise des composés de la formule générale I dans laquelle R^3 représente un atome d'halogène et des amines secondaires de la formule générale $HN(R^4)R^5$ (V), dans laquelle R^4 et R^5 possèdent les significations qui leur ont été attribuées dans la revendication 8.

11. Procédé suivant la revendication 10, caractérisé en ce qu'au cours de l'éventuelle amination subséquente, on utilise de la pipérazine ou de l'homopipérazine à titre d'amines secondaires V et en ce que l'on méthyle ou éthyle le produit de réaction obtenu de la formule générale X



(X)

dans laquelle R^1, R^2 et A possèdent les significations qui leur ont été attribuées dans la revendication 8, et n est égal à 2 ou à 3.

12. Procédé suivant la revendication 8, caractérisé en ce que l'on réalise l'acylation avec des composés de la formule générale Z—CO—A—$N(R^4)R^5$ (IX), dans laquelle A, R^4 et R^5 possèdent les significations qui leur ont été attribuées dans la revendication 8 et Z représente un groupe scindable.

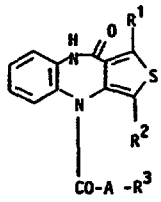
13. Thiénobenzodiazépinones substituées de la formule générale Ia dans laquelle les substituants possèdent les significations qui leur ont été attribuées dans la revendication 7, pour la mise en œuvre du traitement et de la prophylaxie de maladies dues à des affections de l'estomac ou de l'intestin.

* C L M S *

14. Composé suivant la revendication 3, dans lequel R^{1**} représente un atome d'hydrogène, R^{2**} représente le radical méthyle, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un groupe pipérazin-1-yle substitué en position 4 par un radical méthyle et A^{**} représente un radical méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ce composé.

Revendications (pour l'Etat contractant AT)

1. Procédé de préparation de thiénobenzodiazépinones substituées de la formule générale (I)



(I)

dans laquelle

R^1 représente un atome d'hydrogène ou un radical alkyle possédant de 1 à 4 atomes de carbone,

R^2 représente un atome d'halogène ou possède l'une des significations attribuées à R^1,

R^3 représente un atome d'halogène ou le radical $-N(R^4)R^5$ et

R^4 représente un radical alkyle possédant de 1 à 4 atomes de carbone ou un radical alcényle possédant de 3 à 5 atomes de carbone,

R^5 possède l'une des significations attribuées à R^4 ou représente un radical $-(CH_2)_m-N(R^6)R^7$, ou bien

R^4 et R^5 représentent en commun avec l'atome d'azote auquel ils sont attachés, un groupe morpholino, un groupe pyrrolidino, un groupe pipéridino, un groupe hexahydroazépin-1-yle, un groupe pipérazin-1-yle éventuellement substitué en position 4 par un radical méthyle, éthyle ou benzyle, un groupe 2,4-diméthylpipérazin-1-yle ou un groupe hexahydro-1H-1,4-diazépin-1-yle substitué en position 4 par un radical méthyle ou éthyle et

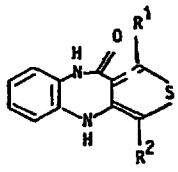
R^6 représente un groupe alkyle possédant de 1 à 4 atomes de carbone,

R^7 représente un groupe alkyle possédant de 1 à 4 atomes de carbone,

A représente un groupe alkylène à chaîne droite ou à chaîne ramifiée possédant de 1 à 5 atomes de carbone et

m est égal à 2 ou à 3,

comme aussi de leurs sels d'addition d'acides, caractérisé en ce que l'on procède à l'acylation de thiénobenzodiazépinones de la formule générale II



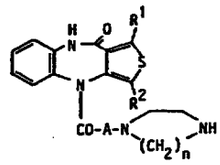
(II)

dans laquelle R^1 et R^2 possèdent les significations qui leur ont été attribuées plus haut et en ce qu'éventuellement l'on soumet les produits ainsi obtenus à une amination et/ou en ce que l'on convertit les bases obtenues en les sels d'addition d'acides ou en ce que l'on transforme les sels d'addition d'acides obtenus en les bases libres ou en les sels d'addition d'acides pharmacologiquement acceptables.

2. Procédé suivant la revendication 1, caractérisé en ce que l'on réalise l'acylation avec des composés de la formule générale Hal—A—CO—Hal' (III) ou $(Hal—A—CO)_2O$ (IV) dans laquelle Hal et Hal' représentent des atomes d'halogène et A représente un groupe alkylène possédant de 1 à 5 atomes de carbone.

3. Procédé suivant la revendication 1, caractérisé en ce qu'au cours de l'éventuelle amination subséquente, on utilise des composés de la formule générale I dans laquelle R^3 représente un atome d'halogène et des amines secondaires de la formule générale $HN(R^4)R^5$ (V), dans laquelle R^4 et R^5 possèdent les significations qui leur ont été attribuées dans la revendication 1.

4. Procédé suivant la revendication 3, caractérisé en ce qu'au cours de l'éventuelle amination subséquente, on utilise de la pipérazine ou de l'homopipérazine à titre d'amines secondaires V et en ce que l'on méthyle ou éthyle le produit de réaction obtenu de la formule générale X

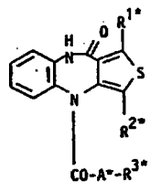


(X)

dans laquelle R^1, R^2 et A possèdent les significations qui leur ont été attribuées dans la revendication 1, et n est égal à 2 ou à 3.

5. Procédé suivant la revendication 1, caractérisé en ce que l'on réalise l'acylation avec des composés de la formule générale Z—CO—A—N(R^4)R^5 (IX), dans laquelle A, R^4 et R^5 possèdent les significations qui leur ont été attribuées dans la revendication 1 et Z représente un groupe scindable.

6. Procédé suivant les revendications 1 et 2, caractérisé en ce que l'on prépare des thiénobenzodiazépinones substituées de la formule générale I*



(I*)

dans laquelle

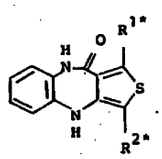
R^{1*} représente un atome d'hydrogène, un radical méthyle ou éthyle,

R^{2*} représente un atome de chlore ou possède l'une des significations attribuées à R^{1*},

R^{3*} représente un atome de chlore, et

A^* représente un groupe alkylène à chaîne droite ou à chaîne ramifiée possédant 1 ou 2 atomes de carbone,

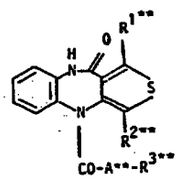
par la réaction de thiénobenzodiazépinones de la formule générale II*



(II*)

dans laquelle R^{1*} et R^{2*} possèdent les significations qui leur ont été précédemment attribuées, sur des dérivés d'acides III* Cl—A^*—CO—Cl (III*) ou IV* (Cl—A^*—CO)$_2$O (IV*) dans laquelle A^* possède les significations qui lui ont été précédemment attribuées.

7. Procédé suivant les revendications 1 et 3, caractérisé en ce que l'on prépare des thiénobenzodiazépinones substituées de la formule générale I**

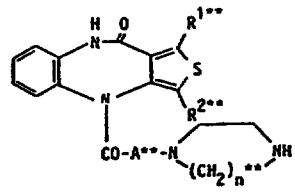


(I**)

dans laquelle

R^{1**} représente un atome d'hydrogène, un radical méthyle ou éthyle,

R^{2**} représente un atome de chlore ou possède l'une des significations attribuées à R^{1**},

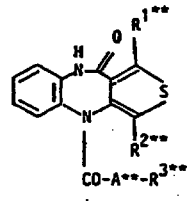


(X**)

dans laquelle R^{1**}, R^{2**} et A^{**} possèdent les significations qui leur ont été précédemment attribuées et n^{**} est égal à 2 ou à 3.

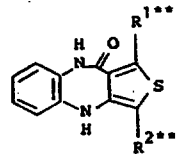
12. Procédé suivant la revendication 11, caractérisé en ce que l'on prépare des composés de la formule générale I^{**} dans laquelle R^{1**} représente un atome d'hydrogène ou le radical méthyle, R^{2**} possède l'une des significations attribuées à R^{1**}, R^{3**} représente le groupe $—N(R^{4**})R^{5**}$, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un groupe pipérazin-1-yle substitué par un groupe méthyle en position 4 et A^{**} représente un groupe méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.

13. Procédé suivant les revendications 1 et 5, caractérisé en ce que l'on prépare des thiénobenzodiazépinones substituées de la formule générale I^{**}



(I^{**})

dans laquelle R^{1**}, R^{2**}, R^{3**} et A^{**} possèdent les significations qui leur ont été attribuées dans la revendication 7, par la réaction de thiénobenzodiazépinones de la formule générale II^{**}



(II^{**})

dans laquelle R^{1**} et R^{2**} possèdent les significations qui leur ont été précédemment attribuées, sur des dérivés d'acides réactifs de la formule générale IX^{**} $Z^{**}—CO—A^{**}—N—(R^{4**})R^{5**}$ (IX^{**}), dans laquelle Z^{**} représente un groupe scindable et A^{**}, R^{4**} et R^{5**} possèdent les significations qui leur ont été attribuées dans la revendication 7.

14. Procédé suivant la revendication 7, caractérisé en ce que l'on prépare le composé de la formule générale I^{**} dans laquelle R^{1**} représente un atome d'hydrogène, R^{2**} représente le radical méthyle, R^{3**} représente le groupe $—N(R^{4**})R^{5**}$, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un radical pipérazin-1-yle substitué par un groupe méthyle en position 4 et A^{**} représente un groupe méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.

15. Procédé suivant la revendication 11, caractérisé en ce que l'on prépare le composé de la formule générale I^{**} dans laquelle R^{1**} représente un atome d'hydrogène, R^{2**} représente le radical méthyle, R^{3**} représente le groupe $—N(R^{4**})R^{5**}$, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un radical pipérazin-1-yle substitué par un groupe méthyle en position 4 et A^{**} représente un groupe méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.

16. Procédé suivant la revendication 13, caractérisé en ce que l'on prépare le composé de la formule générale I^{**} dans laquelle R^{1**} représente un atome d'hydrogène, R^{2**} représente le radical méthyle, R^{3**} représente le groupe $—N(R^{4**})R^{5**}$, R^{4**} et R^{5**} représentent, communément avec l'atome d'azote, un radical pipérazin-1-yle substitué par un radical méthyle en position 4 et A^{**} représente un radical méthylène, comme aussi les sels d'addition d'acides pharmacologiquement acceptables de ces composés.