

PATENT SPECIFICATION

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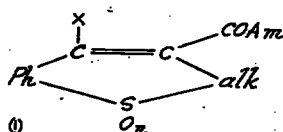
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(54) NEW 2,3-DIHYDRO-1-BENZOTHIEPIN-4-CARBOXAMIDES, PROCESS FOR THEIR MANUFACTURE AND PHARMACEUTICAL PREPARATIONS CONTAINING THEM

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns the manufacture of 2,3 - dihydro - 1 - benzothiepin - 4 - carboxamides of the general formula I



wherein Ph is 1,2-phenylene optionally substituted by one or more members selected from lower alkyl, lower alkoxy, lower alkylthio, halogeno, trifluoromethyl, cyano or nitro, X is hydroxy, lower alkoxy, lower alkanoyloxy, di-lower alkylamino or lower alkyleneimino, Am is amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, lower alkyleneimino, lower mono- aza-, mono- oxa- or mono- thia-alkyleneimino, cycloalkylamino, H - Ph - amino, N-lower alkyl - H - Ph - amino, (H-Ph represents a phenyl radical optionally substituted as for the radical Ph), Hc-amino or N-lower alkyl - Hc - amino, wherein Hc is a heterocyclic residue of aromatic character selected from furyl, thienyl, pyrrol, 1,2- or 1,3-oxazolyl or -thiazolyl, pyrazolyl, imidazolyl, pyridyl, pyridazinyl,

pyrimidyl or pyrazinyl, or the lower alkyl derivatives thereof, "alk" is lower alkylene separating the adjacent sulfur from the carbon atom attached to —COAm by two carbon atoms and n is 0, 1 or 2, or a salt, especially a therapeutically useful salt thereof.

The 1,2-phenylene radical Ph is unsubstituted or substituted by one or more than one, preferably by one or two, of the same or different members selected from the group consisting of lower alkyl, e.g. methyl, ethyl, n- or i-propyl or -butyl; lower alkoxy, e.g. methoxy, ethoxy, n- or i-propoxy or -butoxy; lower alkylthio, e.g. methyl- or ethylthio; or halogeno, e.g. fluoro, chloro or bromo; trifluoromethyl, cyano or nitro.

The term "lower", referred to above and hereinafter in connection with organic radicals or compounds respectively, defines such with up to 7, preferably up to 4, carbon atoms. When "lower" qualifies "alkylene", it defines such radicals with at least two carbon atoms.

Preferred 1,2-phenylene radicals Ph are 1,2-phenylene, (lower alkyl) - 1,2 - phenylene, (lower alkoxy) - 1,2 - phenylene, (lower alkylthio) - 1,2 - phenylene, mono- or di- (halogeno) - 1,2 - phenylene or (trifluoromethyl) - 1,2 - phenylene.

When X is hydroxy, the compounds of the invention are depicted by Formula I as the tautomeric enols (derived from the corresponding 5-ketones), rendering them acidic to form salts with bases, especially therapeutically useful salts. When X is lower alkoxy, or alkanoyloxy, e.g. acetoxy, propionyloxy or pivalyloxy, said formula depicts enolethers

or -esters, and when X is either of the two tert. amino groups, the formula depicts enamines, which are no longer acidic.

The amino group Am and said tert. amino group X are exemplified by amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, e.g. mono- or di(methyl, ethyl, n- or i-propyl or -butyl; 2-hydroxyethyl or 2- or 3-hydroxypropyl)-amino; lower alkyleneimino, e.g. pyrrolidino, piperidino, 1,4-, 1,5-, 1,6-, 2,5-, 2,6- or 1,7-hexylene or -heptyleneimino; lower mono-aza-, mono-oxa- or monothiaalkyleneimino, e.g. piperazino, homopiperazino, morpholino or thiomorpholino. Cycloalkyl-amino is preferably 3 to 7 ring-membered, e.g. cyclopropylamino, cyclopentylamino or cyclohexylamino and the (H-Ph (as defined above) or Hc)-amino or N-lower alkyl-N-(H-Ph or Hc)-amino groups are illustrated, by (phenyl, tolyl, anisyl, methylthiophenyl, mono- or di-fluoro or mono- or di-chlorophenyl, bromophenyl, trifluoromethylphenyl, cyanophenyl or nitrophenyl; 2- or 3-furyl, -thienyl or -pyrryl, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4-pyridyl, 4-pyridazinyl, 2-pyrimidyl or 2-pyrazinyl)-amino, or the N-methylated tert. amino and/or ring-methylated analogs thereof.

The lower alkylene group "alk" represents preferably 1,2-ethylene, but also 1,2-propylene, 1,2- or 2,3-butylene, 1,2- or 2,3-pentylene.

Therapeutically useful bases for the formation of salts with said enols (X=OH) are preferably alkali metal hydroxides, ammonia or amines illustrated by H-Am or lower alkyl-Am, e.g. sodium, potassium, ammonium, mono-, di or trimethyl or -ethyl-ammonium, pyrrolidinium, morpholinium, anilinium or 2-pyridylammonium salts.

The compounds of the invention exhibit valuable pharmacological properties, primarily anti-inflammatory activity. This can be demonstrated by in-vitro or in-vivo tests, using for the latter advantageously mammals, such as rats or dogs, as test objects. The compounds of the invention can be administered to the animals either enterally, preferably orally, parenterally, e.g. subcutaneously or intravenously, or topically, for example in the form of aqueous or oily solutions or starchy suspensions. The applied dosage may range between about 0.1 and 200 mg/kg/day, preferably between about 1 and 100 mg/kg/day, advantageously between about 5 and 50 mg/kg/day. The tests chosen are among the classical assay methods for said activity, such as the carrageenin paw-edema, or adjuvant arthritis test in rats, or more recent tests described by Perper et al in Arthritis Rheum. 17, 47 (1974). There ³⁵S-labelled rabbit ear cartilage degradation is induced by the non-phagocytic release of neutral proteases from viable human leukocytes. Anti-rheumatic agents prevent this enzyme-release at concen-

trations correlated with their blood levels usually achieved in man. In addition, the compounds of the invention inhibit the neutral proteases themselves.

Thus, for example, the N - (4 - fluoro-phenyl, 2,4- or 3,4 - dichlorophenyl) - 7 - chloro - 5 - (hydroxy or pyrrolidino) - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamides, representative members of the compounds of Formula I, are highly active in rats at p.o. doses as low as 1 mg/kg/day in the paw-edema and adjuvant arthritis essay and prevent at very low concentrations the ³⁵S - enzyme - release from viable human leukocytes in vitro. Accordingly, the compounds of the invention are useful anti-inflammatory agents, for example in the treatment or management of arthritic and dermatopathologic conditions.

Particularly useful are compounds of the general Formula I, wherein Ph is 1,2-phenylene, unsubstituted or substituted by one or two of the same or different members selected from lower alkyl, lower alkoxy, lower alkylthio, halogeno, trifluoromethyl, cyano or nitro, X is hydroxy, lower alkoxy, lower alkanoyloxy, di-lower alkylamino or lower alkyleneimino, Am is amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, lower alkyleneimino, piperazino, 4-lower alkylpiperazino, morpholino, thiomorpholino, 3 to 7 ring-membered cycloalkylamino, H - Ph - amino, (H-Ph being as defined above), N-lower alkyl - H - Ph - amino, Hc-amino or N-lower alkyl - Hc - amino, wherein Hc is a heterocyclic residue of aromatic character selected from furyl, thienyl, pyrryl, 1,2- or 1,3-oxazolyl or -thiazolyl, pyrazolyl, imidazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl, or the lower alkylated derivatives thereof, "alk" is lower alkylene separating the adjacent sulfur from the carbon atom by two carbon atoms and n is an integer from 0 to 2, or a salt thereof derived from a therapeutically useful base.

Preferred compounds of the invention are those of the general Formula I, wherein Ph is 1,2-phenylene, (lower alkyl) - 1,2 - phenylene, (lower alkoxy) - 1,2 - phenylene, (lower alkylthio) - 1,2 - phenylene, mono- or di - (halogeno) - 1,2 - phenylene or (trifluoromethyl) - 1,2 - phenylene, X is hydroxy, lower alkanoyloxy, di-lower alkylamino or 5 to 7 ring-membered lower alkyleneimino, Am is mono- or di-lower alkylamino, 5 to 7 ring-membered lower alkyleneimino, 5 to 7 ring-membered cycloalkylamino, H - Ph - amino (H-Ph being as defined above) or Hc-amino, wherein Hc is 2- or 3-furyl, -thienyl or -pyrryl, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4-pyridyl, 4-pyridazinyl, 2-pyrimidyl or 2-pyrazinyl, or the ring-monomethylated derivatives thereof, "alk" is 1,2-ethylene or 1,2-propylene and

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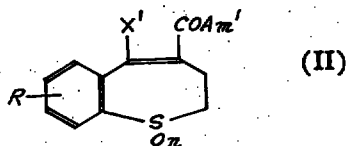
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n is an integer from 0 to 2, or a salt thereof derived from a therapeutically useful base.

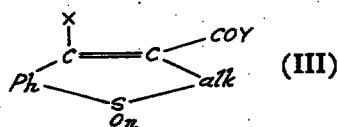
Outstanding are compounds of the general Formula II



wherein R is methyl, *t*-butyl, methoxy, methylthio, fluoro, chloro, bromo or trifluoromethyl, X' is hydroxy, acetoxy, pyrrolidino or piperidino, Am' is (phenyl, tolyl, anisyl, methylthiophenyl, mono- or di-fluoro or mono- or dichlorophenyl, bromophenyl, trifluoromethylphenyl, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4 - pyridyl) - amino, and n is 0, 1 or 2, or the sodium, potassium, ammonium, mono-, di or trimethyl- or -ethylammonium, pyrrolidinium, morpholinium or H-Am salt thereof.

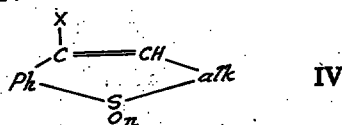
Especially valuable are those compounds of the general Formula II, wherein R is chlorine in the 7-position, X' is hydroxy or pyrrolidino, Am is mono- or di-fluoro- or mono- or dichlorophenylamino and n is 0, 1 or 2, or the sodium, potassium, ammonium, mono-, di- or trimethyl- or -ethylammonium, pyrrolidinium, morpholinium, anilinium or 2-pyridylammonium salt thereof.

The compounds of the invention are prepared according to conventional methods, for example by a) reacting a corresponding 2,3 - dihydro - 1 - benzothiepin - 4 - carboxylic acid ester of Formula III



wherein Y is lower alkoxy, with the amine H-Am or

b) adding to a corresponding 4 - unsubstituted 2,3 - dihydro - 1 - benzothiepin of Formula IV



in which X is di-lower alkylamino, lower alkyleneimino or a group OY, wherein Y represents an alkali metal atom, the isocyanate Am''=CO, wherein Am''H is a primary or secondary amino group selected from Am and, if desired, converting a resulting enol ether or enamine into the corresponding enol by acidic hydrolysis, and/or, converting a resulting enol into its salt by reaction with a base or an alkali metal hydride, and/or,

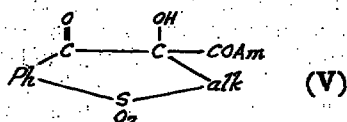
acylating a resulting enol-salt to an enol ester defined above, and/or, converting a resulting enol of the general formula I by reaction with a di-lower alkylamine or a lower alkyleneimine into an enamine of the formula I shown above, and/or, oxidizing a resulting compound of the general formula I shown above, in which n represents 0 or 1 to the corresponding 1-oxide or 1,1-dioxide.

The amination according to item a) is carried out in the usual manner, advantageously between about room temperature and about 200°, with equivalent amounts of the ester used. The lower alkanol, generated in the reaction with said esters, is preferably distilled off together with diluent, such as an aromatic hydrocarbon, e.g. benzene, toluene or xylene.

The addition of the isocyanate according to item b) is preferably carried out with compounds of Formula III wherein X is an alkali metal salt of the enolic hydroxy group, or wherein X is advantageously said tert.-amino, and an equivalent amount or slight excess of the isocyanate, preferably between about room temperature and about 100°C and the presence of a polar solvent, such as an ether, e.g. diethyl ether or tetrahydrofuran.

The compounds of Formula I, so obtained, can be converted into each other according to methods known per se. Thus, for example, the enols (X=OH) can be obtained from the enol ethers (X=alkoxy) or preferably the enamines (X=di-lower alkylamino or lower alkyleneimino) by acidic hydrolysis, advantageously with the use of hydrohalic acids. The resulting enols can be salified with said therapeutically useful bases or alkali metal hydrides, advantageously in the presence of an alcoholic solvent, such as a lower alkanol, e.g. ethanol, or an ether, e.g. tetrahydrofuran, or an amide, e.g. dimethylformamide, at moderate temperatures, e.g. below 100°C. Resulting salts may also be acylated, for example with lower alkanoyl halides, e.g. acetyl chloride, to yield said enol esters. When said enols are reacted with di-lower alkylamines or lower alkyleneimines at raised temperatures and for a longer period of time, the enamines of Formula I are obtained. Said enols with n=0 can also be oxidized to the corresponding 1-oxides or 1,1-dioxides with the use of mild or strong oxidants, such as periodates, e.g. sodium periodate in said polar solvents and at low temperatures, e.g. between about 0°C and room temperature for the former, or hydrogen peroxide or organic peracids, such as lower peralkanoic or perbenzoic acids, e.g. peracetic or m-chloroperbenzoic acid, advantageously at temperatures at or below room temperature with the latter, or up to 100°C with diluted hydrogen peroxide in the presence of lower alkanolic acids, e.g. acetic acid. Care should be taken,

especially with said peracids, in order to prevent overoxidation at overly long reaction times, yielding compounds of Formula V



5 with similar pharmacological effects as those of Formula I.

The starting materials used are known or, if new, can be prepared according to the methods used for the known analogs or illustrated by the examples herein. Thus, esters of Formula III are described in Collection Czechoslov. Chem. Commun. Vol. 37, p. 1195 (1972) and compounds of Formula IV in J. Org. Chem. 26, 2728 (1961) or J. Chem. Soc. (c), 1971, p. 2252. An isocyanate starting material may be formed from the corresponding acid oxide.

The above reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or neutralizing agents and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, at atmospheric or superatmospheric pressure.

In the process of the invention those starting materials are advantageously selected, which yield the above-described preferred embodiments of the invention, especially those corresponding to Formula II.

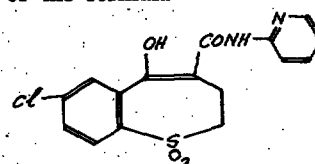
The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions containing an effective amount thereof in conjunction or admixture with excipients suitable for either enteral, parenteral or topical application. Preferred are tablets and gelatin capsules comprising the active ingredient together with diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethylene-glycol; for tablets also binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, e.g. starches, agar, alginic acid or its sodium salt, enzymes of the binders or effervescent mixtures and/or absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically valuable substances. Said pharmaceutical compositions

are prepared according to conventional mixing, granulating or coating methods respectively and contain about 0.1 to 75% by weight, preferably about 1 to 50% of the active ingredient.

The following examples illustrating the invention are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade. If not specified, all evaporations are carried out under reduced pressure.

Example 1.

A stirred solution of 8 g of 7-chloro-5-hydroxy-2,3-dihydro-1-benzothiepin-1,1-dioxide-4-carboxylic acid methyl ester, 2.5 g of 2-aminopyridine and 160 ml of dry toluene is refluxed for 6 hours, while 30 ml of the solvent is distilled off and replaced by the same amount of toluene. After about 5 hours the mixture is cooled, filtered, and the solid washed with toluene. It is heated with 50 ml of ethanol, the mixture filtered while hot and the residue collected, to yield the N-(2-pyridyl)-7-chloro-5-hydroxy-2,3-dihydro-1-benzothiepin-1,1-dioxide-4-carboxamide of the formula



melting at 211—213°.

The ethanolic filtrate is evaporated and the residue recrystallized from ethanol to yield a small amount of the 2-pyridylammonium salt of said amide melting at 171—174°.

The starting material is prepared as follows: A mixture of 31 g of 7-chloro-5-hydroxy-2,3-dihydro-1-benzothiepin (Brit. Patent 1,112,681), 126 ml of acetic acid and 77.7 ml of 30% aqueous hydrogen peroxide is left at room temperature overnight, swirled, then heated on a steam bath for 1 hour. The mixture is cooled, swirled, and poured into 600 ml of ice-water. It is filtered, the solid rinsed with 1000 ml of water and dried, to yield the 7-chloro-5-hydroxy-2,3-dihydro-1-benzothiepin-1,1-dioxide melting at 166—168°.

A mixture of 9.4 g of 7-chloro-5-hydroxy-2,3-dihydro-1-benzothiepin-1,1-dioxide, 4 g of pyrrolidine, 0.01 g of p-toluenesulfonic acid and 100 ml of dry benzene is refluxed for 4 days on a water trap until the theoretical amount of water is collected. Thereupon it is evaporated, to yield the 7-chloro-5-pyrrolidino-2,3-dihydro-1-benzothiepin-1,1-dioxide about 90% pure. (The analogously prepared 7-unsubstituted compound boils at 190°/0.15 mmHg, whereas the 7-chloro-5-piperidino-analog melts at 108—112°.)

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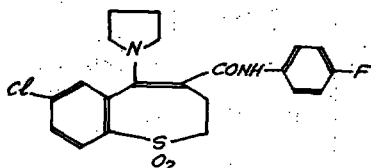
A solution of 26.8 g of 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide in 360 ml of dry tetrahydrofuran is taken and 14.8 ml of triethylamine is added during 35 minutes to the mixture of 86.4 ml of 12.5% phosgene in benzene and 54 ml of dry tetrahydrofuran while stirring at -15° . The mixture is allowed to warm to room temperature and stirred for 3 hours, to yield a solution of 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxylic acid chloride useful for the amination according to a).

It is treated with a solution of 14.8 ml of triethylamine and 210 ml of methanol during 10 minutes, whereby the temperature rises to 34° . The mixture is stirred at room temperature for 1 hour, refluxed for 13 hours and concentrated to one-half its volume. The concentrate is diluted with 360 ml of water, extracted with chloroform, the extract washed with water, dried and evaporated, to yield the 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxylic acid methyl ester.

A mixture of 32 g of 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxylic acid methyl ester, 30 ml of 6N aqueous hydrochloric acid and 300 ml of methanol is refluxed for 1.25 hours and the precipitate collected after cooling, to yield the 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxylic acid methyl ester melting at $150-152^{\circ}$ (The analogously prepared 7-unsubstituted ester melts at $140-143^{\circ}$).

Example 2.

To a solution of 6 g of 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide in 6 ml of dry tetrahydrofuran is added 2.8 g of p-fluorophenylisocyanate in 6 ml of tetrahydrofuran dropwise while stirring under nitrogen. The mixture is held at $40-45^{\circ}$ for one hour, at room temperature for one hour and then cooled to 0° with an ice-bath. It is filtered, the solid rinsed with cold tetrahydrofuran, triturated with cold diethyl ether and recrystallized from acetonitrile or ethyl acetate, yielding N - (p - fluorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide of the formula



melting at $163-165^{\circ}$.

Example 3.

A mixture of 6 g of N - (p - fluoro-

phenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide and 60 ml of ethanol is treated at room temperature with 6 ml of 6N hydrochloric acid in one portion while stirring. It is refluxed for one hour and left overnight at room temperature. It is cooled in an ice-bath and the precipitate collected, to yield the N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at $167-169^{\circ}$.

A mixture of 3.5 g of N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide and 20 ml of ethanol is treated with 3 ml of pyrrolidine in one portion. A reaction is evidenced by a color change from colorless to yellow and the formation of a homogeneous solution. The mixture is refluxed for two minutes, cooled, treated with 10 ml of diethyl ether, the precipitate formed filtered off and rinsed with diethyl ether to yield the corresponding pyrrolidinium salt melting at $175-177^{\circ}$. The analogously prepared morpholinium salt melts at 193 to 196° .

Example 4.

According to the method shown in Example 2, the N - (p - fluorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1 - oxide - 4 - carboxamide is prepared from equivalent amounts of the corresponding reagents, it melts at $189-190^{\circ}$.

It can be hydrolyzed as shown in Example 3, to yield the N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1 - oxide - 4 - carboxamide, melting at $218-219^{\circ}$ with decomposition.

The starting material is prepared as follows: A solution of 6.4 g of 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin in 65 ml of dry methanol and 65 ml of dry dioxane is treated dropwise at 0° in 1 hour with a solution of 7 g of sodium metaperiodate in 65 ml water. The mixture is stirred at 0° for two hours after the addition period and then allowed to warm to room temperature overnight. It is filtered and the solid rinsed with 30 ml of methanol. The combined filtrate and wash is concentrated to a smaller volume and treated with 40 ml of water. The mixture is extracted with chloroform, the extract separated, washed with water, dried and evaporated, to yield the 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1 - oxide boiling at $154-157^{\circ}\text{C}/0.25\text{ mmHg}$.

It is converted into the 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1 - oxide as described in Example 1.

Example 5.

According to the methods illustrated by the previous examples the following com-

pounds of Formula II are prepared from equivalent amounts of the corresponding reagents: Am' = NH-Z, R' is in 7-position; Pyr = pyrrolidino, Pip = piperidino.

No.	Z	X'	R	n	m.p. °C	recryst. from
1	2-thiazolyl	OH	H	0	205-208	benzene
2	"	"	H	2	252-254	-
3	"	"	Cl	0	211-213	acetone
4	"	"	Cl	2	230-231	-
5	5-CH ₃ -3-isoxazolyl	"	Cl	2	210-212	-
6	2,4-F ₂ -C ₆ H ₃	"	Cl	2	201-203	-
7	n-butyl	Pyr	Cl	2	149-151	-
8	cyclohexyl	"	Cl	2	165-167	CH ₃ CN
9	phenyl	"	H	0	125-128	-
10	4-F-C ₆ H ₄	"	Cl	0	149-150	-
11	4-CH ₃ O-C ₆ H ₄	"	Cl	2	147-149	CH ₃ CN
12	4-CH ₃ S-C ₆ H ₄	"	Cl	2	162-164	-
13	2-F-C ₆ H ₄	"	Cl	2	160-162	-
14	4-F-C ₆ H ₄	Pip	Cl	2	168-171	-
15	"	Pyr	H	0	145-147	ethanol
16	4-Cl-C ₆ H ₄	"	H	2	134-137	"
17	"	"	H	0	106-108	benzene
18	4-Br-C ₆ H ₄	"	H	0	109-112	"
19	2-CF ₃ -C ₆ H ₄	"	H	0	115-116	ethanol
20	2,5-F ₂ -C ₆ H ₃	"	Cl	2	153-155	-
21	3-Cl-4-F-C ₆ H ₃	"	Cl	2	136-138	CH ₃ CN
22	phenyl	OH	H	0	165-167	-
23	4-CH ₃ S-C ₆ H ₄	"	Cl	2	205-207	-
24	2-F-C ₆ H ₄	"	Cl	2	141-143	-
25	4-F-C ₆ H ₄	"	H	0	202-204	-
26	"	"	Cl	0	160-163	-
27	"	"	H	2	193-195	ethanol
28	4-Cl-C ₆ H ₄	"	H	0	196-198	-
29	4-Br-C ₆ H ₄	"	H	0	200-201	-
30	2-CF ₃ -C ₆ H ₄	"	H	0	78-81	isopropanol

No.	Z	X'	R	n	m.p. °C	recryst. from
31	2,5-F ₂ -C ₆ H ₃	"	Cl	2	175-177	-
32	3-Cl-4-F-C ₆ H ₃	"	Cl	2	213-215	-
33	4-CH ₃ O-C ₆ H ₄	OH	Cl	2	188-190	methanol
34	phenyl	Pyr.	Cl	2	83-85	(CH ₂) ₄ O
35	4-CH ₃ -C ₆ H ₄	"	Cl	2	152-154	CH ₃ CN
36	3-F-C ₆ H ₄	"	Cl	2	102-105	(CH ₂) ₄ O
37	4-Cl-C ₆ H ₄	"	Cl	2	172-175	-
38	4-Br-C ₆ H ₄	"	Cl	2	169-172	-

Example 6.

To a solution of 8 g of N - (p - fluoro-phenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 4 - carboxamide in 430 ml of chloroform, is added 9.9 g of 87% m-chloroperbenzoic acid in 120 ml of chloroform during 10 minutes while stirring at -5°. The reaction mixture is allowed to warm up to room temperature and stirred overnight. The mixture is washed with saturated aqueous sodium bicarbonate solution, water, saturated aqueous sodium chloride solution, dried, filtered and evaporated. The residue is heated with ethanol and the insoluble material is filtered after cooling to yield the N - (p - fluoro-phenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 203-5°, it is identical in all respects, except for its crystalline form and melting point, with the material of Example 3.

The 7 - deschloro - analog thereof melts at 182-184°, and is identical in all respects to the somewhat purer compound No. 27 of Example 5.

Evaporation of the above filtrate and recrystallization from ethanol gives the N - (p - fluoro-phenyl) - 7 - chloro - 4 - hydroxy - 5 - oxo - 2,3,4,5 - tetrahydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, m.p. 175-177°. The amorphous 7 - deschloro - 5 - oxo analog and the N - (p - chlorophenyl) - 4 - hydroxy - 5 - oxo - 2,3,4,5 - tetrahydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, m.p. 184-185°, are obtained in a similar manner.

A solution of 1 g of N - (p - fluoro-phenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide in 63 ml of chloroform, when treated with the solution of 0.5 g of 87% m-chloroperbenzoic acid in 5 ml of chloroform in the above manner and the reaction mixture worked up in the same way, affords the N - (p - fluoro-phenyl) - 7 - chloro - 4 - hydroxy -

5 - oxo - 2,3,4,5 - tetrahydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, m.p. 166-8° (trituated with ethanol only, instead of recrystallization).

Example 7.

Preparation of 10,000 tablets each containing 100 mg of the active ingredient:

Formula:

N-(p-fluorophenyl)-7-chloro-5-pyrrolidino-2,3-dihydro-1-benzothiepin-1,1-dioxide-4-carboxamide	1,000 g	
Lactose	2,535 g	60
Corn starch	125 g	
Polyethylene glycol 6,000	150 g	
Talcum powder	150 g	
Magnesium stearate	40 g	
Purified water	q.s.	65

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 260 ml of water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm openings and compressed into tablets using concave punches with 10.3 mm diameter, upper bisected.

Analogously tablets are prepared, containing one of the other compounds illustrated by the previous or following examples.

Example 8.

To a solution of 1 g of 7 - chloro - 5 - dimethylamino - 2,3 - dihydro - 1 - benzo-

(15)

thiepin - 1,1 - dioxide in 3 ml of dry tetrahydrofuran is added 0.51 g of p-fluorophenylisocyanate in 2 ml of tetrahydrofuran and the mixture refluxed for 4 hours. It is concentrated, filtered and the residue washed with cold tetrahydrofuran, to yield the N - (p-fluorophenyl) - 7 - chloro - 5 - dimethylamino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 179—181°.

The starting material is prepared as follows: To a stirred suspension of 1.09 g of 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide in 20 ml of benzene a solution of 0.5 g of titanium tetrachloride in 10 ml of benzene is added dropwise while cooling with ice, and the mixture stirred for 1/2 hour at 0°. Thereupon a solution of 0.7 g of dimethylamine in 10 ml of benzene is added dropwise and the mixture allowed to warm up to room temperature. It is filtered, the filtrate evaporated, and the residue recrystallized from diethyl ether, to yield the 7 - chloro - 5 - dimethylamino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide melting at 93—95°.

Example 9.

A stirred mixture of 0.3 g of sodium hydride in 20 ml of dry tetrahydrofuran is treated over 1 hour at 0 to -5° with a suspension of 2.1 g of 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide in 26 ml of the same solvent. The mixture turns yellow and bubbling occurs after 45 minutes. After the evolution of hydrogen ceases, the mixture is treated in one portion with 3.1 g of p-fluorophenyl - isocyanate dissolved in 7 ml of the same solvent at 0°. It is allowed to come to 25° in about 1 hour, stirred and poured into 50 ml of ice-water and filtered. The filtrate is acidified with concentrated hydrochloric acid, a yellow oil separates, which solidifies on cooling. It is filtered off and recrystallized from ethanol, to yield the N - (p - fluorophenyl) - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 193—195°; it is identical with compound No. 27 of Example 5.

Example 10.

A stirred solution of 182 g of 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide in 180 ml of dry tetrahydrofuran is treated dropwise over 45 minutes, beginning at 20°, with a solution of 115 g of 3,4-dichlorophenylisocyanate in 125 ml of the same solvent. The mixture warms to about 48° during the addition period and is allowed to cool to ambient temperature over night whereupon a solid precipitates. Filtering and washing it with a small amount of tetrahydrofuran and recrystallizing it therefrom affords the N - (3,4 - dichlorophenyl) -

7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 123—124°.

Example 11.

A mixture of 10 g of N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, 100 ml of 95% ethanol and 10 ml of 6N aqueous hydrochloric acid is refluxed for 45 minutes during which a solid precipitates. It is filtered off and washed with a small amount of ethanol, to yield the N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 235—236°.

A solution of 7.7 g N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide in 70 ml of anhydrous ethanol and 7.5 ml of pyrrolidine is refluxed for 30 minutes, cooled and diluted with diethyl ether until precipitation of the solid ceases. After one hour it is filtered, to yield the corresponding pyrrolidinium salt melting at 195—197°.

Example 12.

A stirred solution of 15 g of 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide in 15 ml of dry tetrahydrofuran is treated within 5 minutes, beginning at 20°, with a solution of 9.4 g of 2,4-dichlorophenylisocyanate in 15 ml of the same solvent. The mixture warms to about 35° during the addition period and after 45 minutes it is heated at 40—50° for 30 minutes, cooled to 20°, and evaporated. The oily residue is triturated with acetonitrile, to yield the N - (2,4 - dichlorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 148—151°.

Example 13.

A mixture of 10 g of N - (2,4 - dichlorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, 100 ml of 95% ethanol, and 10 ml of 6N aqueous hydrochloric acid is refluxed for 45 minutes and cooled to 20° whereupon a solid precipitates. It is filtered, the filtrate concentrated to one half its original volume, again filtered and the combined residue washed with ethanol, to yield the N - (2,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 140—142°.

A solution of 7.1 g of N - (2,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide in 75 ml of anhydrous ethanol and 7.5 ml of pyrrolidine is refluxed for 30

65

70

75

80

85

90

95

100

105

110

115

120

125

16

minutes and a yellow solid precipitates. The mixture is cooled to 20°, mixed with 50 ml of diethyl ether, filtered and washed with diethyl ether as solvent to yield the corresponding pyrrolidinium salt melting at 187—188°.

Example 14.

A stirred suspension of 0.4 g of sodium hydride in 6 ml of dimethylformamide is treated dropwise over 25 minutes with a solution of 3.5 g of N - (p - fluorophenyl) - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide in 6 ml of the same solvent. After the gas evolution has ceased, 0.68 ml of acetyl chloride in 2 ml of dimethylformamide are added within 10 minutes and stirred at 20° for 1.5 hours. It is poured into a mixture of 30 ml of ice-water and 6 ml of concentrated hydrochloric acid, whereupon the precipitate filtered off and dissolved in 180 ml of methylene chloride. The solution is washed twice with water, dried, evaporated and the residue triturated with methanol, to yield the N - (p - fluorophenyl) - 5 - acetoxy - 2,3 - dihydro -

1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide melting at 175—177°.

Example 15.

According to the methods illustrated by Examples 10 and 11, the following compounds are prepared from equivalent amounts of the corresponding starting material: N - (p - fluoro- or chloro - phenyl) - 8 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, m.p. 148—149° or 175—177° respectively, after recrystallization from acetonitrile, and the N - (p - fluoro- or chlorophenyl) - 8 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide, m.p. 193—195° or 215—217° respectively, their pyrrolidinium salts melt at 187—188° or 197—198° respectively.

Example 16.

According to the methods illustrated by the previous examples, the following compounds of Formula II are prepared from equivalent amounts of the corresponding reagents: Am' = NH—Z, R is in 7-position; Pyr = pyrrolidino;

(17)

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1,500,744

10

No.	Z	X'	R	n	m.p. °C	Pyr.-salt m.p. °C
1	4-F-C ₆ H ₄	Pyr.	CH ₃	2	148-150A	—
2	4-Cl-C ₆ H ₄	„	„	2	123-125	—
3	4-F-C ₆ H ₄	„	t.C ₄ H ₉	2	196-198	—
4	„	„	F	2	1560, 1580 cm ⁻¹ I.R.	—
5	2-F-C ₆ H ₄	„	Cl	1	214-216	—
6	2,6-Cl ₂ -C ₆ H ₃	„	„	2	1570, 1655 cm ⁻¹ I.R.	—
7	4-F-C ₆ H ₄	OH	CH ₃	2	219-220	144-145
8	4-Cl-C ₆ H ₄	„	„	2	222-224	173-175
9	4-F-C ₆ H ₄	„	t.C ₄ H ₉	2	179-182	194-196
10	4-F-C ₆ H ₄	„	F	2	192-194	163-164
11	2-F-C ₆ H ₄	„	Cl	1	—	186
12	„	„	„	2	141-143	194-195
13	3F-C ₆ H ₄	„	„	1	—	168-169A
14	„	„	„	2	187-189	197-198
15	4-Cl-C ₆ H ₄	„	„	1	218-219	175-176
16	„	„	„	2	256-257	190-191
17	2,6-Cl ₂ -C ₆ H ₃	„	„	2	126-127B	175-177
18	2,4-F ₂ -C ₆ H ₃	„	„	2	201-203	173-175
19	2,5-F ₂ -C ₆ H ₃	„	„	2	175-177	194-195
20	3-Cl-4-F-C ₆ H ₃	„	„	2	213-215	159-161
21	4-CH ₃ -C ₆ H ₄	„	„	2	205-207	185-187
22	C ₆ H ₅	„	„	2	173-175	204-205
23	cyclohexyl	„	„	2	163-166	169-170
24	3-pyridyl	„	„	2	213-214	190-191
25	3-CH ₃ -2-pyridyl	„	„	2	176-178	185-186
26	5-Cl-2-pyridyl	„	„	2	211-212	195-196
27	2-pyrimidinyl	„	„	2	250	188-190
28	2-pyrazinyl	„	„	2	200-202C	193-194

A=acetonitrile

B=methanol

C=ethylacetate for recrystallization.

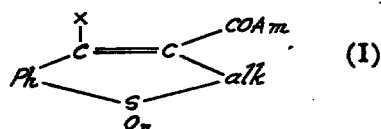
Example 17.

A mixture of 8 g of N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide in 100 ml of 95% aqueous ethanol is treated in one portion with a solution of 0.7 g of sodium hydroxide in 15 ml of methanol while stirring at room temperature. The mixture is warmed to 50° and allowed to cool to room temperature during 1 hour. It is filtered, the filtrate evaporated and the residue triturated with ethanol/diethyl ether (1:9), to yield the corresponding sodium salt monohydrate melting at 225° with decomposition.

Analogously the sodium salt monohydrate of the N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide is prepared, melting at 260° with decomposition.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



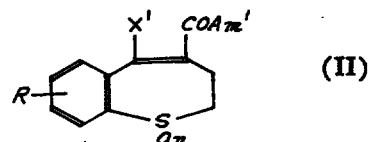
wherein Ph is 1,2-phenylene optionally substituted by one or more members selected from lower alkyl, lower alkoxy, lower alkylthio, halogeno, trifluoromethyl, cyano or nitro, X is hydroxy, lower alkoxy, lower alkanoyloxy, di-lower alkylamino or lower alkyleneimino, Am is amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, lower alkyleneimino, lower mono-aza-, mono-oxa- or mono-thia-alkyleneimino, cycloalkylamino, H - Ph - amino, N-lower alkyl - H - Ph - amino, wherein H-Ph represents a phenyl radical optionally substituted as for radical Ph, Hc-amino or N-lower alkyl - Hc - amino, wherein Hc is a heterocyclic residue of aromatic character selected from furyl, thienyl, pyrrol, 1,2- or 1,3-oxazolyl or -thiazolyl, pyrazolyl, imidazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl, or the lower alkyl derivatives thereof, "alk" is lower alkylene separating the adjacent sulfur from the carbon atom shown by two carbon atoms and n is 0, 1 or 2.

2. A compound of the general formula I shown in claim 1, wherein Ph is 1,2-phenylene, unsubstituted or substituted by one or two of the same or different members selected from lower alkyl, lower alkoxy, lower alkylthio, halogeno, trifluoromethyl, cyano or nitro, X is hydroxy, lower alkoxy, lower alkanoyloxy, di-lower alkylamino or lower alkyleneimino, Am is amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, lower alkyleneimino, piperazino, 4-lower alkylpiperazino, morpholino, thiomorpholino, 3 to 7 ring-membered

cycloalkylamino, H - Ph - amino, N-lower alkyl - H - Ph - amino, Hc-amino or N-lower alkyl - Hc - amino, wherein Hc is a heterocyclic residue of aromatic character selected from furyl, thienyl, pyrrol, 1,2- or 1,3-oxazolyl or -thiazolyl, pyrazolyl, imidazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl, or the lower alkyl derivatives thereof, "alk" is lower alkylene separating the adjacent sulfur from the carbon atom shown by two carbon atoms and n is an integer from 0 to 2.

3. A compound of the general formula I shown in claim 1, wherein Ph is 1,2-phenylene, (lower alkyl) - 1,2 - phenylene, (lower alkoxy) - 1,2 - phenylene, (lower alkylthio) - 1,2 - phenylene, mono- or di- (halogeno) - 1,2 - phenylene or (trifluoromethyl) - 1,2 - phenylene, X is hydroxy, lower alkanoyloxy, or 5 to 7 ring-membered lower alkyleneimino, Am is mono- or di-lower alkylamino, 5 to 7 ring-membered lower alkyleneimino, 5 to 7 ring-membered cycloalkylamino, H - Ph - amino or Hc-amino, wherein Hc is 2- or 3-furyl, -thienyl or -pyrrol, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4-pyridyl, 4-pyridazinyl, 2-pyrimidyl or 2-pyrazinyl, or the ring-monomethylated derivatives thereof, "alk" is 1,2-ethylene or 1,2-propylene and n is an integer from 0 to 2.

4. A compound of the general Formula II



wherein R is methyl, t. butyl, methoxy, methylthio, fluoro, chloro, bromo or trifluoromethyl, X' is hydroxy, acetoxy, pyrrolidino or piperidino, Am' is (phenyl, tolyl, anisyl, methylthiophenyl, mono- or di-fluoro or mono- or dichlorophenyl, bromophenyl, trifluoromethylphenyl, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4 - pyridyl) - amino, and n is an integer from 0 to 2.

5. A compound of the general formula II shown in claim 4 and enumerated in Example 16.

6. A compound of the general formula II shown in claim 4, wherein R is chlorine in the 7-position, X' is hydroxy or pyrrolidino, Am' is mono- or di-fluoro- or mono- or dichlorophenylamino and n is an integer from 0 to 2.

7. A compound of the general formula I shown in claim 1, wherein X represents hydroxy, lower alkoxy, di-lower alkylamino or lower alkyleneimino, and the other symbols have the meanings given in claim 1.



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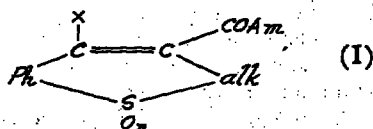
Example 17.

A mixture of 8 g of N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide in 100 ml of 95% aqueous ethanol is treated in one portion with a solution of 0.7 g of sodium hydroxide in 15 ml of methanol while stirring at room temperature. The mixture is warmed to 50° and allowed to cool to room temperature during 1 hour. It is filtered, the filtrate evaporated and the residue triturated with ethanol/diethyl ether (1:9), to yield the corresponding sodium salt monohydrate melting at 225° with decomposition.

Analogously the sodium salt monohydrate of the N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide is prepared, melting at 260° with decomposition.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



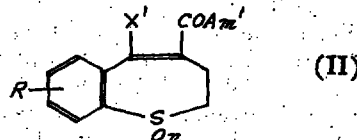
wherein Ph is 1,2-phenylene optionally substituted by one or more members selected from lower alkyl, lower alkoxy, lower alkylthio, halogeno, trifluoromethyl, cyano or nitro, X is hydroxy, lower alkoxy, lower alkanoyloxy, di-lower alkylamino or lower alkyleneimino, Am is amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, lower alkyleneimino, lower mono-aza-, mono-oxa- or mono-thia-alkyleneimino, cycloalkylamino, H - Ph - amino, N-lower alkyl - H - Ph - amino, wherein H-Ph represents a phenyl radical optionally substituted as for radical Ph, Hc-amino or N-lower alkyl - Hc - amino, wherein Hc is a heterocyclic residue of aromatic character selected from furyl, thienyl, pyreryl, 1,2- or 1,3-oxazolyl or -thiazolyl, pyrazolyl, imidazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl, or the lower alkyl derivatives thereof, "alk" is lower alkylene separating the adjacent sulfur from the carbon atom shown by two carbon atoms and n is 0, 1 or 2.

2. A compound of the general formula I shown in claim 1, wherein Ph is 1,2-phenylene, unsubstituted or substituted by one or two of the same or different members selected from lower alkyl, lower alkoxy, lower alkylthio, halogeno, trifluoromethyl, cyano or nitro, X is hydroxy, lower alkoxy, lower alkanoyloxy, di-lower alkylamino or lower alkyleneimino, Am is amino, mono- or di-(lower alkyl or hydroxyalkyl)-amino, lower alkyleneimino, piperazino, 4-lower alkylpiperazino, morpholino, thiomorpholino, 3 to 7 ring-membered

cycloalkylamino, H - Ph - amino, N-lower alkyl - H - Ph - amino, Hc-amino or N-lower alkyl - Hc - amino, wherein Hc is a heterocyclic residue of aromatic character selected from furyl, thienyl, pyreryl, 1,2- or 1,3-oxazolyl or -thiazolyl, pyrazolyl, imidazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl, or the lower alkyl derivatives thereof, "alk" is lower alkylene separating the adjacent sulfur from the carbon atom shown by two carbon atoms and n is an integer from 0 to 2.

3. A compound of the general formula I shown in claim 1, wherein Ph is 1,2-phenylene, (lower alkyl) - 1,2 - phenylene, (lower alkoxy) - 1,2 - phenylene, (lower alkylthio) - 1,2 - phenylene, mono- or di- (halogeno) - 1,2 - phenylene or (trifluoromethyl) - 1,2 - phenylene, X is hydroxy, lower alkanoyloxy, or 5 to 7 ring-membered lower alkyleneimino, Am is mono- or di-lower alkylamino, 5 to 7 ring-membered lower alkyleneimino, 5 to 7 ring-membered cycloalkylamino, H - Ph - amino or Hc-amino, wherein Hc is 2- or 3-furyl, -thienyl or -pyreryl, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4-pyridyl, 4-pyridazinyl, 2-pyrimidyl or 2-pyrazinyl, or the ring-monomethylated derivatives thereof, "alk" is 1,2-ethylene or 1,2-propylene and n is an integer from 0 to 2.

4. A compound of the general Formula II



wherein R is methyl, t. butyl, methoxy, methylthio, fluoro, chloro, bromo or trifluoromethyl, X' is hydroxy, acetoxy, pyrrolidino or piperidino, Am' is (phenyl, tolyl, anisyl, methylthiophenyl, mono- or di-fluoro or mono- or dichlorophenyl, bromophenyl, trifluoromethylphenyl, 5 - methyl - 3 - 1,2 - oxazolyl or -thiazolyl, 2 - 1,3 - oxazolyl or -thiazolyl, 3-pyrazolyl, 2-imidazolyl, 2-, 3- or 4 - pyridyl) - amino, and n is an integer from 0 to 2.

5. A compound of the general formula II shown in claim 4 and enumerated in Example 16.

6. A compound of the general formula II shown in claim 4, wherein R is chlorine in the 7-position, X' is hydroxy or pyrrolidino, Am' is mono- or di-fluoro- or mono- or dichlorophenylamino and n is an integer from 0 to 2.

7. A compound of the general formula I shown in claim 1, wherein X represents hydroxy, lower alkoxy, di-lower alkylamino or lower alkyleneimino, and the other symbols have the meanings given in claim 1.



8. A compound of the general formula I shown in claim 1, wherein X represents hydroxy, lower alkoxy, di-lower alkylamino or lower alkyleneimino, and the other symbols have the meanings given in claim 2.

9. A compound of the general formula I shown in claim 1, wherein X represents hydroxy, di-lower alkylamino or 5 to 7 ring-membered lower alkyleneimino, and the other symbols have the meanings given in claim 3.

10. A compound of the general formula II shown in claim 4, wherein R represents methyl, methoxy, methylthio, fluoro, chloro, bromo or trifluoromethyl, X' represents hydroxy, pyrrolidino or piperidino, and the other symbols have the meanings given in claim 4.

11. A compound of the general formula II shown in claim 4 and enumerated in Example 5.

12. N - (2 - pyridyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

13. N - (p - fluorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

14. N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

15. N - (p - fluorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1 - oxide - 4 - carboxamide.

16. N - (p - fluorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1 - oxide - 4 - carboxamide.

17. N - (p - fluorophenyl) - 7 - chloro - 5 - dimethylamino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

18. N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

19. N - (3,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

20. N - (2,4 - dichlorophenyl) - 7 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

21. N - (2,4 - dichlorophenyl) - 7 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

22. N - (p - fluorophenyl) - 5 - acetoxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

23. N - (p - fluorophenyl) - 8 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

24. N - (p - fluorophenyl) - 8 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

25. N - (p - chlorophenyl) - 8 - chloro - 5 - pyrrolidino - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

26. N - (p - chlorophenyl) - 8 - chloro - 5 - hydroxy - 2,3 - dihydro - 1 - benzothiepin - 1,1 - dioxide - 4 - carboxamide.

27. A 5-hydroxy compound as claimed in any one of claims 1 to 6, 19, 21, 24 and 26 in the form of a therapeutically acceptable salt derived from a base.

28. A 5-hydroxy compound as claimed in any one of claims 7 to 12, 14 and 16 in the form of a therapeutically acceptable salt derived from a base.

29. A 5-hydroxy compound as claimed in any one of claims 1 to 6, 19, 21, 24 and 26 in the form of the sodium, potassium, ammonium, mono-, di- or trimethylammonium, mono-, di- or triethylammonium, pyrrolidinium, morpholinium or H-Am salt, in which Am has the meaning given in claim 1.

30. A 5-hydroxy compound as claimed in any one of claims 7 to 12, 14 and 16 in the form of the sodium, potassium, ammonium, mono-, di- or trimethylammonium, mono-, di- or triethylammonium, pyrrolidinium, morpholinium or H-Am salt, in which Am has the meaning given in claim 1.

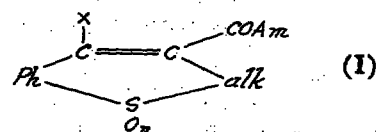
31. A compound as claimed in either of claims 19 and 21 in the form of the sodium or pyrrolidinium salt thereof.

32. A compound as claimed in claim 14 in the form of the sodium or pyrrolidinium salt thereof.

33. A pharmaceutical preparation containing a compound claimed in any one of claims 1 to 6, 18 to 27, 29 and 31.

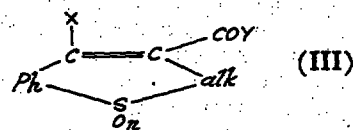
34. A pharmaceutical preparation containing a compound claimed in any one of claims 7 to 17, 28, 30 and 32.

35. Process for the manufacture of 2,3 - dihydro - 1 - benzothiepin - 4 - carboxamides of the general formula I



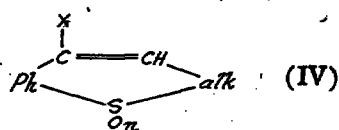
wherein Ph, X, Am, alk, and n are as defined in claim 1, or a salt thereof derived from a base, which consists in

a) reacting a corresponding 2,3 - dihydro - 1 - benzothiepin - 4 - carboxylic acid ester of the general formula III



wherein Y is lower alkoxy, with the amine H-Am or

b) adding to a corresponding 4 - unsubstituted 2,3 - dihydro - 1 - benzothiepin of the general formula IV



in which X is di-lower alkylamino, lower alkyleneimino or a group OY, wherein Y represents an alkali metal atom, the isocyanate Am''=CO, wherein Am''H is a primary or secondary amino group selected from Am and, if desired, converting a resulting enol ether or enamine into the corresponding enol by acidic hydrolysis, and/or, converting a resulting enol into its salt by reaction with a base or an alkali metal hydride, and/or, acylating a resulting enol-salt to an enol ester defined above, and/or, converting a resulting enol of the general formula I by reaction with a di-lower alkylamine or a lower alkyleneimine into an enamine of the formula I shown above, and/or, oxidizing a resulting compound of the general formula I shown above, in which n represents 0 or 1 to the corresponding 1-oxide or 1,1-dioxide.

36. The process claimed in claim 35 and described in any one of examples 9 to 17.

37. The compounds of the general formula I shown in claim 1, prepared according to either of claims 35 and 36.

38. The compounds of the general formula I shown in claim 1, prepared according to any one of examples 9 to 17.

39. Process according to claim 35 for the manufacture of compounds of the general formula I shown in claim 35, in which formula X represents hydroxy, lower alkoxy, di-lower alkylamino or lower alkyleneimino, and the other symbols have the meanings given in claim 35, or a therapeutically useful salt

thereof derived from a base, which consists in

a) reacting a compound of the formula III shown in claim 35, in which X has the meaning given above, with the amine H-Am or

b) adding to a compound of the formula IV shown in claim 35, in which X is di-lower alkylamino or lower alkyleneimino, the isocyanate Am''-CO, wherein Am''H is a primary or secondary amino group selected from Am and, if desired, converting a resulting enol ether or enamine into the corresponding enol by acidic hydrolysis, and/or, converting a resulting enol into its therapeutically useful salt by reaction with a base, and/or, converting a resulting enol of the general formula I by reaction with a di-lower alkylamine or a lower alkyleneimine into an enamine of the formula I shown in claim 35, and/or, oxidizing a resulting compound of the general formula I shown in claim 35, in which n represents 0 or 1 to the corresponding 1-oxide or 1,1-dioxide.

40. The process claimed in claim 39 and described in any one of examples 1 to 6 and 8.

41. The compounds of the general formula I shown in claim 1, prepared according to either of claims 39 and 40.

42. The compounds of the general formula I shown in claim 1, prepared according to any one of examples 1 to 6 and 8.

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