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PATENT SPECIFICATION (11) 1 569 238

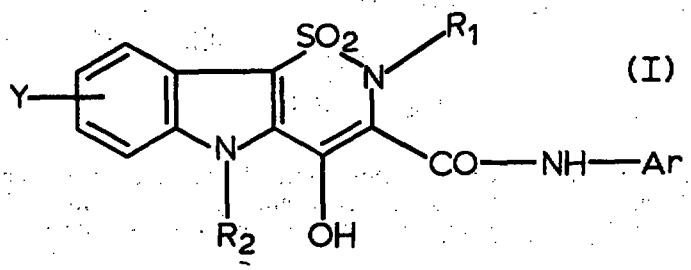
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(54) 2,5-DIHYDRO-1,2-THIAZINO [5,6-B] INDOL-3-CARBOXAMIDE-1,1-DIOXIDE DERIVATIVES

(71) We, DR. KARL THOMAE Gesellschaft mit beschrankter Haftung, a Body Corporate organised under the laws of the Federal Republic of Germany of Biberach an der Riss, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new 2,5-dihydro-1,2-thiazino-[5,6-b]-indol-3-carboxamide-1,1-dioxides, to processes for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention there are provided compounds of general formula I,



(I)

wherein

R_1 represents a hydrogen atom or a methyl or ethyl group;

R_2 represents a methyl or ethyl group;

Y represents a hydrogen, fluorine, chlorine or bromine atom or a methoxy, methyl, ethyl or trifluoromethyl group; and

Ar represents a thiazol-2-yl group (optionally substituted by one or two groups selected from methyl and ethyl groups); a 5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl, 4,5,6,7-tetrahydro-benzothiazol-2-yl or benzothiazol-2-yl group; a pyrid-2-yl group (optionally substituted by a methyl or hydroxy group); a pyrid-3-yl, pyrid-4-yl, pyrimidin-4-yl, pyrazinyl, benzoxazol-2-yl or benzimidazol-2-yl group; an isothiazol-3-yl or oxazol-2-yl group (optionally substituted by a methyl group); or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, trifluoromethyl or methoxy group);

and salts thereof with bases.

The compounds according to the invention possess interesting pharmacological properties and in particular, in general, an antiphlogistic activity and/or a very strong inhibitory effect on blood platelet aggregation.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible salts but other salts with bases may find use, for example, in the preparation of compounds of general formula I and their physiologically compatible salts with bases.

Compounds according to the invention which may be mentioned include, for example compounds of general formula I wherein Ar represents a thiazol-2-yl group, (optionally substituted by one or two groups selected from methyl and ethyl groups); a 5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl, 4,5,6,7-tetrahydrobenzothiazol-2-yl or benzothiazol-2-yl group; a pyrid-2-yl group (optionally substituted by a methyl group) or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, trifluoromethyl or methoxy group) and physiologically compatible salts thereof with bases.

Particularly preferred compounds according to the invention are the following:

2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino - [5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide,

2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl)-1,2 - thiazino[5,6-b]indol - 3 - carboxamide - 1,1 - dioxide,

2,5 - dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol - 2 - yl) - 4 - hydroxy-1,2 - thiazino[5,6-b]indol - 3 - carboxamide - 1,1 - dioxide,

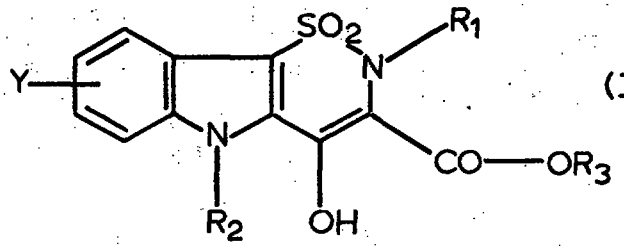
2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methylpyrid - 2 - yl) - 1,2-thiazino-[5,6,b]indol - 3 - carboxamide - 1,1 - dioxide

8 - chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide,

2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - (pyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with bases.

The compounds of general formula I may, for example, be obtained according to the following processes, which processes constitute further features of the present invention:

A. Reaction of a compound of formula II,



(II)

(wherein R_1, R_2 and Y are as hereinbefore defined and R_3 represents an alkyl group containing from 1 to 8 carbon atoms, an aralkyl group containing from 7 to 10 carbon atoms or a phenyl group), with a compound of formula III,

$$NH_2—Ar \qquad (III)$$

(wherein Ar is as hereinbefore defined).

The reaction of the compound of formula II with the compound of formula III is conveniently effected in the presence of an organic solvent inert under the reaction conditions employed e.g. an aromatic hydrocarbon such as e.g. benzene, toluene, xylene, chlorobenzene, *o*-dichlorobenzene or tetrahydronaphthalene; dimethylformamide; dimethylacetamide; dimethylsulfoxide; an ether such as e.g. dimethyoxyethane, diethylene glycol dimethyl ether or diphenyl ether; or an excess of the compound of formula III. Preferred reaction temperatures are from 60 to 200°C. Optionally the reaction may be carried out in an aromatic hydrocarbon e.g. toluene or xylene or an ether and the alcohol formed during the reaction may be separated continuously from the reaction mixture e.g by azeotropic distillation or

by heating under reflux using a Soxhlet extractor equipped with a molecular sieve. The pure product in general crystallizes directly out of the reaction mixture or may be obtained by evaporation of the solvent or when a solvent that is miscible with water is used, it may be precipitated by addition of water. If in the reaction, 2-aminothiazole is used as the compound of formula III, in order to avoid decomposition of this compound, the reaction is desirably carried out in the presence of a catalytic amount of a trialkyl borate, such as e.g. tri-n-butyl borate, triphenylphosphine or of a mixture thereof and/or under nitrogen.

B. for the preparation of compounds of general formula I wherein R_1 represents a methyl or ethyl group: Reaction of a compound of formula I as hereinbefore defined (wherein R_1 represents a hydrogen atom) with a compound of formula IV,

$$R_1'—Hal \qquad (IV)$$

(wherein R_1' represents a methyl or ethyl group and Hal represents a halogen atom) in the presence of a base.

Reaction temperatures are preferably from 0 to 80°C.

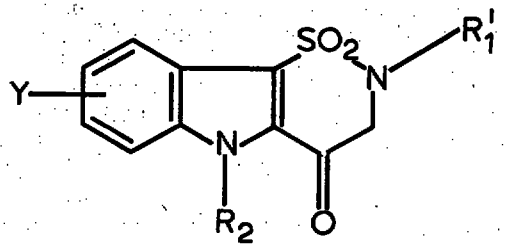
The base may, for example, be an alkali or alkaline earth metal hydroxide, e.g. potassium, sodium or barium hydroxide; an alkali or alkaline earth metal carbonate, e.g. potassium or sodium carbonate; an alkali or alkaline earth metal alcoholate, e.g. sodium ethylate, sodium methylate, potassium methylate or potassium tert. butylate; or a tertiary amine, e.g. triethylamine. With such bases the reaction is desirably carried out in an aqueous medium, in an alcoholic medium, for example in methanol, ethanol, n-propanol or isopropanol or in mixtures thereof.

Other possible solvents include, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide and hexamethylphosphoric acid triamide. When an alkali or alkaline earth metal carbonate is used as the base, then aliphatic ketones, such as e.g. acetone may also be used as solvents.

The compound of formula IV, for example, a bromide or iodide, when in an alcoholic solution, may be added directly to the other components of the reaction mixture. In the case of methyl bromide, it is in general necessary to use a closed vessel.

Alternatively, if the reaction is effected in the presence of an organic solvent such as aromatic hydrocarbon, e.g. benzene or an open-chain or cyclic ether, e.g. tetrahydrofuran, an alkali metal hydride or alkaline earth metal hydride, e.g. sodium hydride, can be used as the base. In such cases, the alkyl halide of formula IV is added only after the reaction of the base with the compound of formula IV is complete.

C. for the preparation of compounds of general formula I wherein R_1 represent a methyl or ethyl group and Ar represents a benzimidazol-2-yl or benzoxazol-2-yl group; an oxazol-2-yl group (optionally substituted by a methyl group) or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl trifluoromethyl or methoxy group).
Reaction of a compound of formula V



(V)

(wherein R_1', R_2 and Y as hereinbefore defined) with a compound of formula VI,

$$Ar'—N=C=O \qquad (VI)$$

[wherein Ar' represents a benzimidazol-2-yl or benzoxazol-2-yl group; an oxazol-2-yl group (optionally substituted by a methyl group) or a phenyl group (optionally

substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl or trifluoromethyl or methoxy group)] in the presence of a base or of a Grignard reagent.

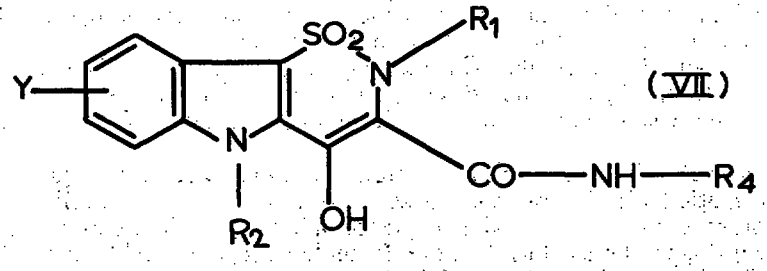
Tertiary amines, such as, for example, triethylamine and 1,5-diazabicyclo[4,3—0]non-5-ene can be used as the base. However, preferred bases are alkali metal hydrides and alkaline earth metal hydrides, most preferably used in substantially equimolar quantities as compared with the compound of formula VI. Sodium hydride has provded particularly suitable.

When a base is present aprotic organic solvents may conveniently be used, such as, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide, hexamethylphosphoric acid triamide, tetrahydrofuran, 1,4-dioxan or aromatic hydrocarbons e.g. benzene. The base and the compound of formula VI are preferably used in molar excess with respect to the compound of formula V. The reaction is preferably carried out at temperatures of from ambient temperature to the boiling temperature of the reaction mixture.

Advantageously when a base is used the reaction is carried out by dissolving the compound of formula V in one of above-mentioned organic solvents and subsequently adding an equivalent quantity of an alkali metal hydride or alkaline earth metal hydride and the compound of formula VI, thereto.

When a Grignard reagent, such as e.g. an alkyl magnesium halide, is present, the reaction is also preferably effected in an inert organic solvent such as an ether. Preferred solvents are diethyl ether, dibutyl ether, tetrahydrofuran, anisole and mixtures thereof. Preferred reaction temperatures in this case are from −20 to +150°C, most preferably 0 to 30°C.

D. Reaction of a compound of formula VII,



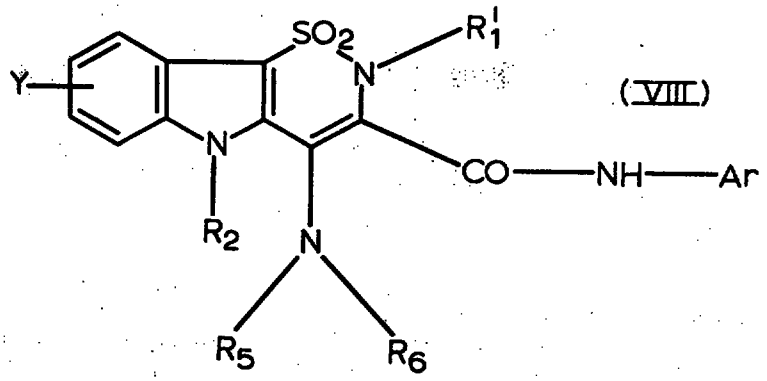
(VII)

(wherein R_1, R_2 and Y are as hereinbefore defined and R_4 represents a hydrogen atom, an alkyl group containing from 1 to 8 carbon atoms, a cycloalkyl group containing from 3 to 10 carbon atoms, an aralkyl group containing from 7 to 10 carbon atoms or a phenyl group) with a compound of formula III as hereinbefore defined.

The reaction is preferably carried out in the presence of an aromatic hydrocarbon, e.g. benzene, toluene, xylene or *o*-dichlorobenzene; dimethylformamide; dimethylacetamide; dimethylsulfoxide; hexamethylphosphoric acid triamide; an ether e.g. dimethoxyethane, diethylene glycol dimethyl ether or diphenyl ether; or an excess of the compound of formula III as solvent. The reaction is preferably carried out at temperatures of from 80 to 200°C. In a preferred embodiment the compound of formula VII is dissolved in xylene at the boiling temperature of the reaction mixture, then catalytic quantities of *p*-toluenesulfonic acid are added thereto followed by the compound of formula III used in excess. Either the product crystallizes directly from the reaction mixture or it may be obtained by evaporation of the solvent. It may alsternatively be precipitated, when using a solvent miscible with water, by addition of water.

E. for the preparation of compounds of general formula I wherein R_1 represents a methyl or ethyl group:

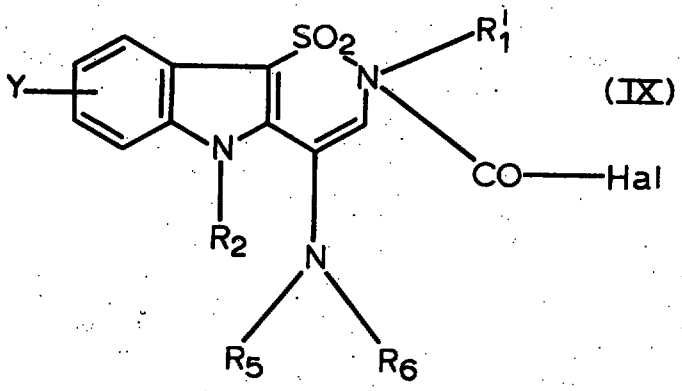
Hydrolysis of a compound of formula VIII



(wherein Y, R_2, Ar and R_1' are as hereinbefore defined and either R_5 and R_6, which may be the same or different, each represents an alkyl group containing from 1 to 3 carbon atoms or, together with the nitrogen atom to which they are attached, they represent a piperidino, pyrrolidino, morpholino, or N-methylpiperazino group), whereby the desired compound of formula I is obtained.

Hydrolysis may, for example, be effected by heating the compound of formula VIII in the presence of an aqueous or aqueous-alcoholic solution of a strong or medium strong acid, for example, a hydrohalic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, *p*-toluenesulfonic acid, trifluoroacetic acid or mixtures thereof. Hydrohalic acids, glacial acetic acid and aqueous acetic acid are preferred.

The compound of formula VIII may be obtained, if desired, preferably *in situ*, by reaction of a compound of formula IX

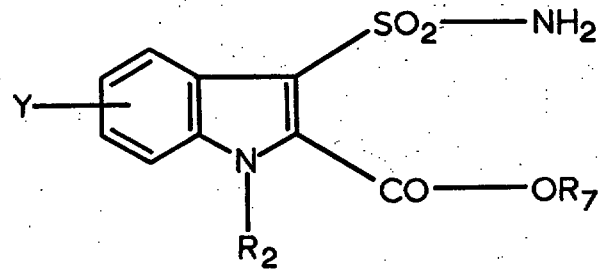


(wherein Y, R_2, R_1', R_5 and R_6 are as hereinbefore defined and Hal represents a halogen atom) with a compound of formula III as hereinbefore defined.

The reaction of the compound of formula IX with the compound of formula III is preferably carried out in the presence of an aromatic hydrocarbon or ether as solvent and preferably at temperatures of from −40°C to +80°C. The reaction may also optionally be effected in the presence of a tertiary organic base such as e.g. triethylamine.

The compounds of general formula I may, if desired, be converted into their physiologically compatible salts by reaction with appropriate bases, suitable methods being well known in the art. Alkali metal alcoholates, alkali metal hydroxides, alkaline earth metal hydroxides, trialkylammonium hydroxides and alkylamines may, for example, be used as the base.

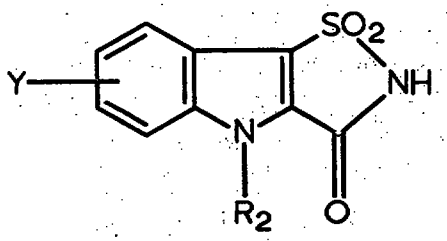
The compounds of general formula II may be obtained for example, from alkyl 3-sulfamoyl-indol-2-carboxylates of general formula X,



(X)

(wherein R_2 and Y are as hereinbefore defined and R_7 represents an alkyl group, such as e.g. a methyl or ethyl group).

Thus an ester of formula X is reacted with an alcohol/alkali metal alcoholate mixture to form an alkali metal salt of a 2H-isothiazolo[4,5-*b*]indol-3(4H)-one-1,1-dioxide of formula Xa,

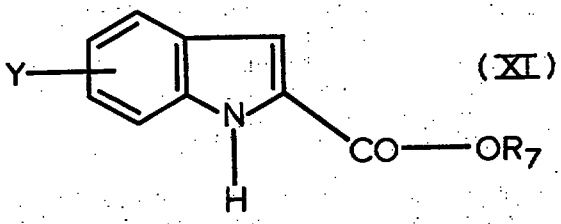


(Xa)

(wherein R_2 and Y are as hereinbefore defined). Such a salt may then be reacted with a halo-acetate, at temperatures of from 100—150°C, to form an ester of 3,4-dihydro-3-oxo-2H-isothiazolo[4,5-*b*]indol-2-acetic acid-1,1-dioxide which ester may subsequently be subjected to a base-catalysed rearrangement reaction by treatment with from 2 to 3 equivalents of an alkali metal alcoholate and subsequent heating. After acidification, a 2,5-dihydro-4-hydroxy-1,2-thiazino[5,6-*b*]indol-3-carboxylic acid-1,1-dioxide ester of formula II is obtained in which R_1 represents a hydrogen atom.

The compounds of general formula II wherein R_1 represents a methyl or ethyl group are obtained therefrom by alkylation with a methyl or ethyl halide either in an alcoholic or aqueous alcoholic solvent using an equivalent of an alkali metal hydroxide or in an aprotic solvent such as e.g. hexamethylphosphoric acid triamide, using an equivalent of an alkali metal hydride.

The compounds of general formula X wherein R_2 and R_7 represent a methyl group and Y represents a hydrogen atom, can be produced according to the method of J. Szmuszkovicz [J. Org. Chem *29*, 178 (1964)]. The other compounds of general formula X may be obtained analogously starting from the known methyl or ethyl indol-2-carboxylates of general formula XI,

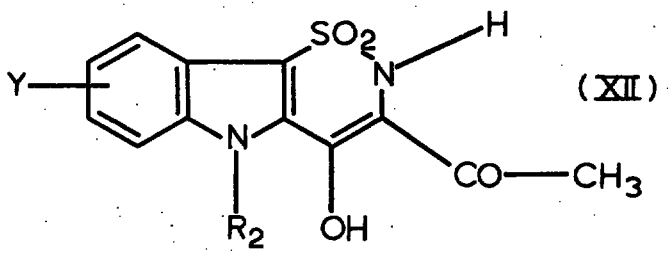


(XI)

(wherein R_7 and Y are as hereinbefore defined) by N-alkylation with a methyl or ethyl halide in a polar aprotic solvent, such as hexamethylphosphoric acid triamide using an equivalent of an alkali metal hydride, followed by reaction with thionyl chloride, treatment with a mixture of ether and liquid ammonia and finally oxidation with potassium permanganate in aqueous acetone. The by-products of this oxidation are the 2H-isothiazolo[4,5-*b*]indol-3(4H)-one-1,1-dioxides of general formula Xa, which can be converted, like the carboxylates of general formula X, into 3,4-dihydro-3-oxo-2H-isothiazolo[4,5-*b*]indol-2-acetic acid-1,1-dioxide esters by treatment with an alcohol/alkali metal alcoholate mixture and subsequent warming in the presence of a haloacetate.

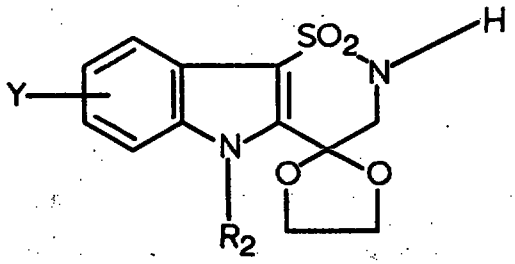
The starting compounds of general formula V may for example be obtained

from the alkali metal salts of a 2H-isothiazolo[4,5-*b*]indol-3(4H)-one-1,1-dioxide of formula Xa by reaction with a haloacetone e.g. chloroacetone, in dimethylsulfoxide and at temperatures of from 100 to 150°C to form a 2-acetonyl-2H-isothiazolo[4,5-*b*]indol-3(H)-one-1,1-dioxide and subsequent base-catalysed rearrangement in the presence of from 2 to 3 equivalents of an alkali metal alcoholate to form a 3-acetyl-2,5-dihydro-4-hydroxy-1,2-thiazino[5,6-*b*]-indol-1,1-dioxide of formula XII,



(XII)

(wherein R_2 and Y are as hereinbefore defined). The acetyl derivative of formula XII may then be treated, in the presence of an acid and under anhydrous conditions, with ethylene glycol to form a ketal of formula XIIa,



(XIIa)

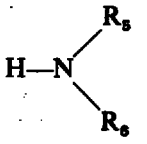
(wherein R_2 and Y are as hereinbefore defined). For example, 3-acetyl-2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino[5,6-*b*]indol-1,1-dioxide may be treated with ethylene glycol in benzene as solvent and in the presence of *p*-toluenesulfonic acid as catalyst for 5 days to form the ethylene ketal of 2,5-dihydro-5-methyl-1,2-thiazino[5,6-*b*]indol-4(3H)-one-1,1-dioxide.

The ketals of general formula XIIa may subsequently be alkylated either with methyl iodide where a compound of formula V wherein R_1' is a methyl group is desired or with ethyl iodide where a compound of formula V wherein R_1' is an ethyl group is desired. The alkylation may be performed in an alcoholic or aqueous alcoholic solvent, using an equivalent of an alkali hydroxide and by subsequent treatment with an acid, for example with aqueous alcoholic hydrochloric acid, whereby the desired 2,5-dihydro-1,2-thiazino[5,6-*b*]indol-4(3H)-one-1,1-dioxide is formed.

The starting compounds of general formula VII wherein R_4 represents a C_{1-8} alkyl, C_{3-10} cycloalkyl, C_{7-10} aralkyl or phenyl group can be obtained, for example, by reaction of a 2,5-dihydro-1,2-thiazino[5,6-*b*]-indol]-4(3H)-one-1,1-dioxide of formula V with an appropriate alkyl isocyanate, cycloalkyl isocyanate, aralkyl isocyanate or phenyl isocyanate, analogously to process C described above.

The compounds of general formula VII wherein R_4 represents a hydrogen atom may be obtained by reaction of a 2,5-dihydro-4-hydroxy-1,2-thiazino[5,6-*b*]indol-3-carboxylic acid-1,1-dioxide ester of formula II with ammonia.

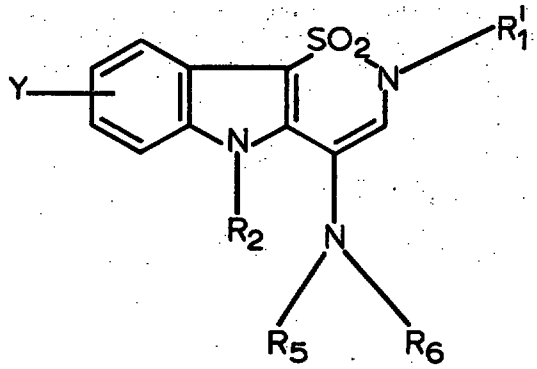
The compounds of general formula VIII can be produced for example by reaction of a 2,5-dihydro-1,2-thiazino[5,6-*b*]indol-4(3H)-one-1,1-dioxide of formula V with a secondary aliphatic amine of formula XIII,



(XIII)

(wherein R_5 and R_6 are as hereinbefore defined), in an organic, inert solvent such

as e.g. benzene or toluene and optionally in the presence of an acid catalyst e.g. *p*-toluenesulfonic acid, the compound of formula XIV,



(XIV)

(wherein R_1', R_2, R_5, R_6 and Y are as hereinbefore defined) thus obtained being subsequently treated with phosgene, preferably in the presence of a tertiary organic base, e.g. triethylamine, in an inert, organic solvent, e.g. tetrahydrofuran, at temperatures of from –50°C and +50°C. The compound of formula IX thus formed may be used directly to form a compound of formula VIII, preferably *in situ*, which may then in turn yield a compound of formula I as described in process E above without further isolation.

As already mentioned above the compounds of general formula I and their physiologically compatible salts with bases possess interesting pharmacological properties. Those compounds which we have tested exhibit an antiphlogistic and/or inhibitory effect on the aggregation of blood-platelets. These compounds are thus in general suitable for the treatment of rheumatic diseases and as antithrombotics.

The pharmacological properties of the compounds according to the invention were determined by means of standard pharmacological tests.

Thus, the following compounds

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[4,5 - *b*]indol - 3 - carboxamide - 1,1 - dioxide = A

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methyl - thiazol-2 - yl) - 1,2 - thiazino[5,6 -*b*]indol - 3 - carboxamide - 1,1-dioxide = B

2,5 - Dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol-2 - yl) - 4 - hydroxy - 1,2 - thiazino[5,6 - *b*]indol - 3 - carboxamide-1,1 - dioxide = C

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methylpyrid-2 - yl) - 1,2 - thiazino[5,6 - *b*]indol - 3 - carboxamide-1,1 - dioxide = D

8 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol-2 - yl) - 1,2 - thiazino[5,6 - *b*]indol - 3 - carboxamide - 1,1-dioxide and = E

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N-(pyrid - 2 - yl) - 1,2 - thiazino[5,6 - *b*]indol - 3 carboxamide-1,1 - dioxide = F

were examined in comparison to
Acetylsalicylic acid = G

with respect to their inhibitory effect on the aggregation of blood-platelets as induced by collagen. A number of these compounds were also examined with respect to their acute toxicity.

a) BORN Test, Collagen-Induced Aggregation

The platelet aggregation was measured according to the method of BORN and CROSS (J. Physiol. *170*, pp. 397 [1964]) in platelet-rich plasm of healthy humans. The decrease in optical density of the platelet suspensions after addition of collagen was measured and registered photometrically. From the angle of inclination of the density curve the velocity of aggregation was determined. The point on the graph showing the greatest light transmission was taken as the "optical density." The quantity of collagen used was sufficient to produce an irreversible aggregation. The values given refer to the "optical density" and denote the percentage change in the light transmission (= % decrease of aggregation) in the presence of the test compound as compared to the control.

The commercial Collagen of Hormon-Chemie Co., Munich, was used. The following table shows the results:

TABLE 1

Test Compound	Concentration [Mol/l]	BORN Test [= % decrease in aggregation]
A	2×10^{-5}	96%
	2×10^{-6}	81%
B	2×10^{-5}	100%
	2×10^{-6}	97%
	2×10^{-7}	42%
C	2×10^{-5}	89%
	2×10^{-6}	82%
D	5×10^{-5}	86%
	5×10^{-6}	60%
E	1×10^{-4}	100%
	1×10^{-5}	86%
	1×10^{-6}	27%
F	1×10^{-4}	85%
	1×10^{-5}	43%
G (control)	3×10^{-5}	45%
	1×10^{-5}	13%

b) Determination of the Acute Toxicity

The acute toxicity was determined in male and female mice after oral administration of the test compound. The test compounds were administered as suspensions in "Tylose" [registered Trade Mark].

The following table shows the number of animals which died within 1,7 and 14 days after administration of the stated dosage.

TABLE 2

Test Compound	Dosage [mg/kg]	Number of Animals in test	Number of Animals which died within: 1 day	7 days	14 days
A	1,000	10	0	0	0
B	1,000	10	0	0	0
D	1.000	10	0	0	0
E	1.000	10	0	0	0

The results in Table 1 shows that the control compound G (acetylsalicylic acid) causes a 50% decrease in aggregation only at a concentration of about 4×10^{-5} mol/l, whereas the test compounds A, B, C, and E cause this 50% decrease at a concentration being at least 1 decimal power lower. For example, compound B causes a 50% decrease in aggregation at a concentration of about $3 = 10^{-7}$ mol/l. Moreover, as Table 2 shows, the compounds A, B, D and E are non-toxic in mice even at high dosages. Clearly therefore these compounds possess a very favourable therapeutical range.

According to a yet further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as hereinbefore defined or a physiologically compatible salt thereof with a base in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible salts with bases may be incorporated into the conventional pharmaceutical preparations, in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Preferred forms include, for example, tablets, coated tablets, gelatin capsules, suspensions, suppositories, and solutions, e.g. for injection.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 10 to 250, preferably from 25 to 100 mg of active ingredient. The oral daily dosage, whcih may be varied according to the compound used, the subject treated and the complain concerned, may, for example, be from 25 to 500, preferably from 50 to 250 mg per day in adults.

The following non-limiting examples serve to illustrate the present invention.

Example 1.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

3.2 g (10 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 1.2 g (12 mmol) of 2-aminothiazole were refluxed together in 150 ml of xylene for 5 hours under nitrogen. The methanol thus formed was separated using a 4Å molecular sieve in a Soxhlet apparatus. After cooling and being allowed to stand overnight, the crystals obtained were filtered off and washed in ether. Yield: 3.6 g (92% of theory) of 2,5-dihydro-2,5-dimethyl-4-hydroxy-N-(thiazol-2-yl)-1,2-thiazino[5,6 - b]indol-3-carboxamide-1,1-dioxide;

M.p.: 260—261°C (decomposition);

1H—NMR ([D_6]-DMSO): $\delta = 8.0 - 7.1$ (m, 6, 6-H to 9-H), 4'-H, 5'-H); 4.17 (s, 3, 5-CH_3); 2.94 (s, 3, 2-CH_3).

$C_{16}H_{14}N_4O_{S2}$ (390.44)

Calc. C 49.22 H 3.55 N 14.42 S 16.43

Found: 49.20 3.61 14.35 16.65

The starting materials may be obtained by the following steps:

a) methyl 3,4 - dihydro - 4 - methyl - 3 - oxo - 2H - isothiazolo - [4,5 - b]indol-2 - acetate - 1,1 - dioxide

53.66 g (0.2 mol) of methyl 1-methyl-3-sulfamoyl-indol-2-carboxylate were added to a solution of 4.6 g (0.2 g-atoms) of sodium in 250 ml of absolute methanol. The resultant mixture was refluxed for 1 hour and, after cooling, the precipitate thus formed was filtered off. The filtrate was evaporated and the residue filtered with suction. The solid material (sodium 4-methyl-2H-isothiazolo[4,5-b]indol-3(4H)-one-1,1-dioxide) was washed several times in ether and then dried (51 g). The resultant product was added to 100 ml of dry dimethylsulfoxide and 26 g (0.24 mol) of methyl chloroacetate were added thereto. The mixture obtained was stirred for 1

hour at room temperature and then heated for 1 hour in an oil bath at 130°C. After subsequent cooling, a solution of 50 g of sodium acetate in 500 ml of water was added to the reaction mixture. The precipitate thus formed was filtered off with suction, washed with ice-water and with a small quantity of icy methanol and ether and dried. Yield: 56 g (91% of theory) of methyl 3,4-dihydro-4-methyl-3-oxo-2H-isothiazole[4,5-b]-indol-2-acetate-1,1-dioxide;
M.p.: 220—221°C (from benzene).

$C_{13}H_{12}N_2O_5S$ (308.32)

	C	H	N	S
Calc.:	50.64	3.92	9.09	10.40
Found:	50.50	3.87	9.31	10.47

b) methyl 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide

40 ml of dry tert. butanol were added to a well mixed suspension of 30.8 g (0.10 mol) of methyl 3,4-dihydro-4-methyl-3-oxo-2H-isothiazolo[4,5-b]indol-2-acetate-1,1-dioxide and 16.2 g (0.30 mol) of sodium methylate in 350 ml of dry toluene, whereby the reaction temperature increased to 35 to 40°C and the mixture obtained became orange. After 30 minutes stirring the mixture was heated in an oil bath at 60°C for 2 hours and 100 ml of ice-water were added to the subsequently cooled reaction mixture. The aqueous phase was separated off and acidified to pH 3—4 by means of hydrochloric acid. The precipitate thus formed was filtered off, washed with ice-water and ice-cold methanol and ether and dried *in vacuo*. Yield: 23.4 g (76% of theory) of methyl 2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino-[5,6-b]indol-3-carboxylate-1,1-dioxide;
M.p.: 213—215°C (from ethyl acetate)

$C_{13}H_{12}N_2O_5S$ (308.32)

	C	H	N	S
Calc.:	50.64	3.92	9.09	10.40
Found:	50.40	4.00	9.00	10.66

c) methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino - [5,6 - b]indol-3 - carboxylate - 1,1 - dioxide

To 40.0 g (0.13 mol) of methyl 2,5 - dihydro - 4 - hydroxy - 5 - methyl-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 56.8 g (0.40 mol) of methyl iodide, suspended in 400 ml of methanol, were added 130 ml of 1 N sodium hydroxide solution. The mixture obtained was stirred for 24 hours at room temperature and, after cooling to 0°C, the precipitate thus formed was filtered off, washed with ice-water and ice-cold methanol and dried *in vacuo* (24.8 g). The mother liquor was evaporated *in vacuo* to 200 ml, brought to pH 5 with hydrochloric acid and mixed with 100 ml of water. After precipitation and washing and drying of the precipitate thus formed another 9.5 g were obtained. Both precipitates were combined and recrystallised from methanol/ethylene chloride to yield 31.0 g (74% of theory) of methyl 2,5-dihydro-2,5-dimethyl-4-hydroxy-1,2-thiazino[5,6-b]indol-3-carboxylate-1,1-dioxide;
M.p.: 189—190°C
^{1}H—NMR ([D$_6$]-DMSO): δ = 12.5 (s, 1, OH), 8.0 (m, 1) and 7.6—7.3 (m, 3; arom. H); 4.13 (s, 3, 5-CH$_3$); 3.97 (s, 3, OCH$_3$); 3.03 (s, 3, 2-CH$_3$);

$C_{14}H_{14}N_2O_5S$ (322.35)

	C	H	N	S
Calc.:	52.16	4.38	8.69	9.95
Found:	52.20	4.31	8.64	9.86

Example 2.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 1 from methyl 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 2-

amino - 4 - methyl - thiazole in a yield of 88% of theory; M.p.: 270°C (decomposition)

$C_{17}H_{16}N_4O_4S_2$ (404.47)

Calc.: C 50.48 H 3.99 N 13.85 S 15.86

Found: 50.50 3.99 14.00 16.05

Example 3.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (5 - methylthiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 1 from methyl 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 2-amino - 5 - methyl - thiazole in a yield of 88% of theory; M.p.: 250°C (decomposition)

$C_{17}H_{16}N_4O_4S_2$ (404.47)

Calc.: C 50.48 H 3.99 N 13.85 S 15.86

Found: 50.50 3.91 13.71 16.08

Example 4.

2,5 - Dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol - 2 -yl) - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 1 from methyl 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 2 - amino - 4,5 - dimethyl - thiazole in a yield of 87% of theory; M.p.: 265°C (decomposition)

$C_{18}H_{18}N_4O_4S_2$ (418.51)

Calc.: C 51.66 H 4.34 N 13.39 S 15.32

Found: 51.50 4.42 13.72 15.17

Example 5.

Analogously to Example 1 the following compounds were prepared from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol-3 - carboxylate - 1,1 - dioxide and 2 - amino - 4 - ethyl - thiazole, 2 - amino-5 - ethyl - thiazole, 2 - amino - 4 - ethyl - 5 - methyl - thiazole, 2 - amino-5 - ethyl - 4 - methyl - thiazole, 2 - amino - 5,6 - dihydro - 4H - cyclopenta[d] - thiazole and 2 - amino - 4,5,6,7 - tetrahydrobenzothiazole respectively:

5.1 N - (4 - ethylthiazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 83% of theory;

5.2 N - (5 - ethylthiazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 95% of theory; M.p.: 238°C (decomposition);

5.3 N - (4 - ethyl - 5 - methyl - thiazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1-dioxide;
Yield: 88% of theory; M.p.: 236—237°C (decomposition);

5.4 N - (5 - ethyl - 4 - methyl - thiazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 91% of theory;

5.5 2,5 - Dihydro - N - (5,6 - dihydro - 4H - cyclopenta[d]thiazol - 2 - yl) - 2,5-dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide -1,1-dioxide;

Yield: 87% of theory; M.p.: 265°C (decomposition);

5.6 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4,5,6,7 - tetrahydrobenzothiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1-dioxide (dimethylacetamide as solvent);
Yield: 94% of theory; M.p.: 254°C (decomposition).

Example 6.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 2 - yl) - 1,2 - thiazino - [5,6-b]indol - 3 - carboxamide - 1,1 - dioxide

3.2 g (10 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 -b]indol - 3 - carboxylate - 1,1 - dioxide and 1.1 g (12 mmol) of 2 - aminopyridine were refluxed together in 200 ml of xylene for 5 hours. The methanol formed was separated off by means of a 4Å molecular sieve, in a Soxhlet apparatus. After cooling and allowing to stand overnight, the crystals obtained were filtered off and washed in ether. Yield: 3.4 g (89% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 2 - yl) - 1,2 - thiazino[5,6-b]indol - 3 - carboxamide - 1,1 - dioxide; M.p.: 232—233°C (decomposition).

$C_{18}H_{16}N_4O_4S$ (384.42)

Calc.:	C 56.24	H 4.19	N 14.58	S 8.34
Found:	55.90	4.28	14.46	8.29

Example 7.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylpyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 6 from methyl 2,5 - dihydro - 2,5-dimethyl - 4 - hydroxyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate-1,1 - dioxide and 2 - amino - 4 - methyl - pyridine in a yield of 91% of theory; M.p.: 250—251°C (decomposition).

Example 8.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methylpyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 6 from methyl 2,5 - dihydro - 2,5-dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1-dioxide and 2 - amino - 6 - methyl - pyridine in a yield of 89% of theory; M.p.: 229°C (decomposition).

Example 9.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino - [5,6 - b]-indol - 3 - carboxamide - 1,1 - dioxide

2.7 g (8.1 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0,9 g of (9.6 mmol) of aniline were refluxed together in 140 ml of xylene for 4 hours. The methanol formed was separated off by means of a 4Å molecular sieve, in a Soxhlet apparatus. After cooling and allowing to stand overnight, the crystals obtained were filtered off and washed in ether. Yield: 2.8 g (90% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino-[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide; M.p.: 269—270°C (decomposition).

$C_{19}H_{17}N_3O_4S$ 383.43)

Calc.:	C 59.52	H 4.47	N 10.96	S 8.36
Found:	59.60	4.62	10.98	8.40

Example 10.

Analogously to Example 9 the following compounds were produced from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol-3 - carboxylate - 1,1 - dioxide and 4 - fluoro - aniline, 3 - chloroaniline, 4-

bromoaniline, *m* - toluidine, *p* - toluidine, 3 - ethylaniline, 3 - trifluoromethylaniline and *o*-anisidine respectively:

10.1 2,5 - Dihydro - 2,5 - dimethyl - N - (4 - fluorophenyl) - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide (chlorobenzene as solvent);
Yield: 72% of theory; M.p.: 271—272°C (decomposition).

10.2 N - (3 - chlorophenyl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 87% of theory; M.p.: 275°C (decomposition).

10.3 N - (4 - bromophenyl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 93% of theory; M.p.: 272°C (decomposition).

10.4 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (tol - 3 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 97% of theory; M.p.: 250°C (decomposition).

10.5 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (tol - 4 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 carboxamide - 1,1 - dioxide *o* - dichlorobenzene as a solvent);
Yield: 72% of theory; M.p.: 267°C (decomposition).

10.6 N - (3 - ethylphenyl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 81% of theory.

10.7 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (3 - trifluoro - methylphenyl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide (diethylene glycol dimethyl ether as solvent);
Yield: 70% of theory; M.p. 233°C (decomposition).

10.8 2,5 - Dihydroxy - 2,5 - dimethyl - 4 - hydroxy - N - (2 - methoxy-phenyl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 98% of theory; M.p.: 230°C (decomposition).

Example 11.

N - (Benzothiazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.0 g (3.1 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.46 g (3.1 mmol) of 2 - aminobenzothiazole were refluxed in 50 ml of xylene for 5 hours. 1.1 g 81% of theory) of N - (benzothiazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl - 4-hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide crystallized out from the hot reaction mixture.
M.p.: 258°C (decomposition).

Example 12.

2,5 - Dihydro - 4 - hydroxy - 5 - methyl - N - (thiazol - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

3.0 g (9.7 mmol) of methyl 2,5 - dihydro - 4 - hydroxy - 5 - methyl-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide, 1.0 g (10 mmol) of 2 - aminothiazole and 150 ml of xylene were refluxed together for 3.5 hours in a Soxhlet apparatus filled with a 4Å molecular sieve. The resultant mixture was filtered and yielded 2.2 g (63% of theory) of crystalline 2,5 - dihydro - 4 - hydroxy-5 - methyl - N - (thiazol - 2 - yl) - 1, 2 - thiazino[5,6 - b]indol - 3 - carboxamide-1,1-dioxide; M.p.: 260°C (decomposition).

Example 13.

2,5 - Dihydro - 4 - hydroxy - 5 - methyl - N - phenyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 12 from methyl 2,5 - dihydro - 4 - hydroxy-

5 - methyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and aniline in 86% of yield;
M.p.: 252°C (decomposition).

Example 14.

2 - Ethyl - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.7 g (5 mmol) of methyl 2 - ethyl - 2,5 - dihydro - 4 - hydroxy - 5 - methyl-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.5 g (5 mmol) of 2 - aminothiazole were refluxed together in 100 ml of xylene for 6 hours. The hot mixture thus obtained was filtered. After cooling, 1.2 g (59% of theory) of 2 - ethyl - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - N - (thiazol - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide crystallized out from the filtrate; M.p.: 224—225°C (decomposition).

The starting material may be obtained by the following reaction:

methyl 2 - ethyl - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino[5,6 - b]indol-3 - carboxylate - 1,1 - dioxide

In small amounts, 0.87 g of a 55% dispersion of sodium hydride in oil (20 mmol) were added to a cooled suspension of 6.2 g (20 mmol) of methyl 2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino[5,6-b]indol-3-carboxylate-1,1-dioxide in 75 ml of hexamethylphosphoric acid triamide. After stirring the mixture obtained for 1.5 hours at room temperature, 10 ml (0.124 mol) of ethyl iodide were added dropwise thereto whilst cooling. After another 18 hours of stirring at room temperature, 200 ml of ice-water were added to the resultant mixture. The mixture thus obtained was extracted several times with ether and the combined ether phases were washed several times with water, dried and evaporated *in vacuo*. The solid residue was treated with a small quantity of cool methanol, filtered and washed with methanol. After recrystallization from methanol/ethylene chloride, 1.9 g (28% of theory) of methyl 2-ethyl-2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino[5,6-b]indol-3-carboxylate-1,1-dioxide were obtained. M.p.: 184°C.

Example 15.

5 - Ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl - N - (thiazol-2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.5 g (45 mmol) of methyl 5 - ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide, 0.5 g (5 mmol) of 2-aminothiazole and 0.1 mg of tri - n - butyl borate were refluxed together in 120 ml of xylene for 6 hours. The hot reaction mixture thus obtained was then filtered and 0.9 g of crude product crystallized out from the filtrate. After evaporation, another 0.9 g of crude product were obtained from the mother liquor. After recrystallization of the crude product from ethylene chloride, 1.3 g (71% of theory) of 5 - ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl - N - (thiazol-2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide were obtained; M.p.: 230°C (decomposition).

$C_{17}H_{16}N_4O_4S_2$ (404.48)

Calc.: C 50.48 H 3.99 N 13.85 S 15.84

Found: 50.20 4.13 13.50 15.90

The starting material may be obtained via the following steps:

a) ethyl 1-ethyl-indol-2-carboxylate

6.2 g of a 55% dispersion of sodium hydride in oil (0.14 mol) were added with steady stirring, to a solution of 25.0 g (0.13 mol) of methyl indol-2-carboxylate in 100 ml of hexamethylphosphoric acid triamide, within 2 hours and at a temperature of 0°C. The resultant mixture was stirred for 3 hours at room temperature and then 20.6 g (0.13 mol) of ethyl iodide were added dropwise to the mixture, cooled to 0°C, such that the reaction temperature did not rise above 25°C. After 10 hours of steady stirring and while still stirring and with cooling, 500 ml of ice-water were added to the mixture. The mixture thus obtained was extracted 5 times with ether. The combined ether extracts were washed with water, treated with activated

charcoal, dried over magnesium sulphate and evaporated. The pure product thus obtained (26 g) was then distilled under a moderately high vacuum (0.015 mm). The oil distilling at 77—78°C was ethyl 1-ethyl-indol-2-carboxylate; Yield: 25.5 g (90% of theory).

b) ethyl 1-ethyl-3-aminosulfinyl-indol-2-carboxylate

In a 500 ml round flask provided with a gas outlet pipe, 60 ml of thionyl chloride were added with steady stirring and in one portion, to 25 g (0.115 mol) of ethyl 1-ethyl-indol-2-carboxylate. After gas evolution had ceased, the mixture obtained was evaporated *in vacuo* at 30°C.

The residue was suspended in a small quantity of dry ether and the suspension formed was filtered under suction then immediately thereafter the residue was added in small quantities to a solution, cooled to –60°C, of 200 ml of condensed ammonia in 500 ml of dry ether. The temperature of the resultant mixture increased to –40°C and was then brought to room temperature within 6 hours and stirred for another 12 hours. Water and ether were then added thereto. The ether phase was separated, washed with water, dried and evaporated *in vacuo*. The crude product thus obtained was recrystallized from petroleum ether (60—80°C). Yield: 28.6 g (89% of theory) of ethyl 1-ethyl-3-aminosulfinyl-indol-3-carboxylate; M.p.: 78—80°C.

c) ethyl 1 - ethyl - 3 - sulfamoyl - indol - 2 - carboxylate and 4 - ethyl-2H - isothiazolo[4,5 - b]indol - 3(4H) - one - 1,1 - dioxide

To a solution of 28.0 g (0.10 mol) of ethyl 1-ethyl-3-aminosulfinyl-indol-2-carboxylate in 1 l of acetone was added dropwise a solution of 15.8 g (0.10 mol) of potassium permanganate in 400 ml of water, with external cooling such that a reaction temperature of 20—23°C was established. The mixture obtained was stirred for 20 hours. The manganese dioxide thus formed was filtered off and washed in water and acetone. The combined filtrates were evaporated *in vacuo* at 30°C to about 250 ml.

The precipitate thus formed was filtered off, washed well with water and dried *in vacuo*. 20.7 g (70% of theory) of ethyl 1-ethyl-3-sulfamoyl-indol-2-carboxylate were obtained; M.p.: 148—149°C.

After acidification with 5 N hydrochloric acid, another precipitate was separated off from the filtrate, washed and dried: 6.0 g (24% of theory) of 4-ethyl-2H-isothiazolo[4,5 - b]indol-3(4H)-one-1,1-dioxide were obtained.

d) methyl 4 - ethyl - 3,4 - dihydro - 3 - oxo - 2H - isothiazolo - [4,5 - b]indol-2 - acetate - 1,1 - dioxide

α) from ethyl 1 - ethyl - 3 - sulfamoyl - indol - 2 - carboxylate

29.6 g (0.1 mol) of ethyl 1-ethyl-1-3-sulfamoyl-indol-2-carboxylate were added to a methanolic sodium methylate solution (2.3 g sodium [0.1 g-atom] in 150 ml of methanol). The mixture obtained was refluxed for 1 hour and then evaporated to dryness. The residue was suspended in 250 ml of ether. The precipitate obtained was filtered off with suction, dried and suspended in 40 ml of dimethylsulfoxide. The resultant suspension was mixed with 10.5 ml (0.12 mol) of methyl chloroacetate and the mixture thus obtained was heated to 130°C for one hour, then mixed, after cooling, with a solution of 10 g of sodium acetate in 150 ml of water. The precipitate thus formed was filtered off with suction and recrystallized from carbon tetrachloride/ethylene chloride. Yield: 19.5 g (60.5% of theory) of methyl 4-ethyl-3,4-dihydro-3-oxo-2H-isothiazolo[4,5-b]indol-2-acetate-1,1-dioxide; M.p.: 176°C.

β) from 4 - ethyl - 2H - isothiazolo[4,5 - b]indol - 3(4H) - one - 1,1 - dioxide

Analogously to Example 15 d(α)5.0 g (20 mmol) of 4 - ethyl - 2H - isothiazolo-[4,5 - b]indol - 3(4H) - one - 1,1 - dioxide were reacted with sodium methylate and methyl chloroacetate to yield 4.0 g (62% of theory) of methyl 4 - ethyl - 3,4 - dihydro - 3 - oxo - 2H - isothiazolo[4,5 - b]indol - 2 - acetate - 1,1 - dioxide; M.p.: 176°C.

e) methyl 5 - ethyl - 2,5 - dihydro - 4 - hydroxy - 1,2 - thiazino - [5,6 - b]indol-3 - carboxylate - 1,1 - dioxide

19.3 g (60 mmol) of methyl 4-ethyl-3,4-dihydro-3-oxo-2H-isothiazolo[4,5-b]indol-2-acetate-1,1-dioxide and 9.7 g (180 mmol) of sodium methylate, suspended in 150 ml of toluene, were mixed, while stirring well with 30 ml of dry tert.-butanol. The mixture obtained was stirred for 30 min. at room temperature and then for 90

min. at 60°C. The resultant mixture was cooled in an ice-bath and treated with 120 ml of ice-water. The organic phase was separated and extracted with water and the aqueous phase was extracted with ether. The combined aqueous phase were then acidified with hydrochloric acid to pH 3. The precipitate thus formed was washed with water, methanol and ether to yield, after recrystallization with ethylene chloride, 8.3 g (43% of theory) of methyl 5-ethyl-2,5-dihydro-4-hydroxy-1,2-thiazino[5,6-b]indol-3-carboxylate-1,1-dioxide;
M.p.: 216°C (decomposition).

f) methyl 5 - ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl - 1,2 - thiazino - [5,6 - b]-indol - 3 - carboxylate - 1,1 - dioxide

8.1 g (25 mmol) of methyl 5 - ethyl - 2,5 - dihydro - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 10.7 g (75 mmol) of methyl iodide, suspended in 150 ml of methanol were mixed with a solution of 1 g (25 mmol) of sodium hydroxide in 30 ml of water. After 24 hours of stirring at room temperature the precipitate thus formed was filtered off, washed and dried. Yield 4.9 g (58% of theory) of methyl 5 - ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide;
M.p.: 154°C.

Example 16.

5 - Ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl - N - (pyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 15 from methyl 5 - ethyl - 2,5 - dihydro - 4-hydroxy - 2 - methyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 2- aminopyridine in 72% of yield;
M.p.: 232°C (decomposition) from xylene.

Example 17.

5 - Ethyl - 2,5 - dihydro - 4 - hydroxy - 2 - methyl - N - phenyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 15 from methyl 5 - ethyl - 2,5-dihydro - 4 - hydroxy - 2 - methyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and aniline in 56% of yield;
M.p.: 268°C (decomposition) from xylene.

Example 18.

8 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

3.0 g (8.4 mmol) of methyl 8 - chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide, 0.9 g (9 mmol) of 2-aminothiazole and 50 mg of tri - n - butyl borate were refluxed together in 300 ml of dry xylene for 6 hours. The methanol formed was separated off using a 4Å molecular sieve in a Soxhlet apparatus. 3.1 g of crystals were separated off from the cooled resultant mixture by filtration and subsequently boiled in a mixture of 100 ml of acetonitrile and 1 ml of glacial acetic acid. After filtration and drying, 2.45 g (68% of theory) of 8 - chloro - 2,5 - dihydro - 2,5 - dimethyl - 4-hydroxy - N - (thiazol - 2 - yl) - 1,2 thiazino - [5,6 - b]indol - 3 - carboxamide - 1,1-dioxide were obtained;
M.p.: 282°C (decomposition).

$C_{16}H_{13}ClN_4O_4S_2$ (424.89)

Calc.: C 45.23 H 3.08 Cl 8.35 H 13.9 S 15.09

Found: 45.30 3.03 8.44 12.97 14.93

The starting material can be obtained via the following steps:

a) ethyl 5-chloro-1-methyl-indol-2-carboxylate

8.7 g (0.2 mol) of a 55% dispersion of sodium hydride in oil were added, within 15 min. at a temperature of 0°C and under nitrogen, to a solution of 40.0 g (0.18 mol) of ethyl 5-chloro-indol-2-carboxylate in 150 ml of hexamethylphosphoric acid triamide. After stirring the mixture obtained for 2.5 hours at room temperature,

35.5 g (0.25 mol) of methyl iodide were added dropwise thereto whilst cooling. After stirring the resultant mixture overnight 1200 ml of ice-water were added thereto while externally cooling with an ice-bath. The mixture obtained was extracted 5 times with 150 ml aliquots of ether. The ether extracts were washed 5 times with water, dried over magnesium sulfate and evaporated *in vacuo*. The crude product was recrystallized from petroleum. 35.8 g (85% of theory) of ethyl 5-chloro-1-methyl-indol-2-carboxylate were obtained. M.p.: 81.5—82°C.

b) ethyl 3-aminosulfinyl-5-chloro-1-methyl-indol-2-carboxylate

To 35.7 g (0.15 mol) of ethyl 5-chloro-1-methylindol-2-carboxylate were added, with steady stirring, 75 ml of thionyl chloride. After 30 min. of stirring at room temperature, 60 ml of ether were added to the mixture obtained. The precipitate thus formed (ethyl 5-chloro-3-chlorosulfinyl-1-methyl-indol-2-carboxylate) was filtered off, washed with ether and added, in small quantities, to a solution of 200 ml of condensed ammonia, cooled to –60°C, in 500 ml of ether. After stirring of the resultant mixture for 1 hour at –60°C, the temperature was slowly increased to +20°C and subsequently stirring was continued overnight.

After the addition of 150 ml of water, the precipitate formed was filtered off, washed with water and ether and dried. Yield: 39 g (86% of theory) of ethyl 3-aminosulfinyl-5-chloro-1-methyl-indol-2-carboxylate;
M.p.: 144°C (decomposition).

c) ethyl 5 - chloro - 1 - methyl - 3 - sulfamoyl - indol - 2 - carboxylate and 7 - chloro-4 - methyl - 2H - isothiazole[4,5 - b]indol - 3 - (4H) - one - 1,1 - dioxide

A solution of 15.8 g (0.1 mol) of potassium permanganate in 300 ml of water was added dropwise over 2.5 hours at 20°C to a solution of 37.6 (0.125 mol) of ethyl 3-aminosulfinyl-5-chloro-1-methyl-indol-2-carboxylate in 2500 ml of acetone. After stirring the mixture obtained overnight at laboratory temperature, the precipitate formed was filtered off and washed with warm water and acetone. The filtrate was evaporated *in vacuo* at 25—30°C to a volume of about 350 ml. The crystallized product formed (ethyl 5-chloro-1-methyl-3-sulfamoyl-indol-2-carboxylate) was filtered off, washed in water and dried.
Yield: 30.5 g (77% of theory); M.p.: 207—208°C.
After acidification to pH 3 another product was obtained from the filtrate: 7-chloro-4-methyl-2H-isothiazolo [4,5-b]indol-3-(4H)-one-1,1-dioxide, which was washed with water and dried. Yield: 3.9 g (12% of theory);
M.p. 288°C (decomposition).

d) methyl 7 - chloro - 3,4 - dihydro - 4 - methyl - 3 - oxo - 2H - isothiazolo-[4,5 - b]indol - 2 - acetate - 1,1 - dioxide

30.5 g (0.096 mol) of ethyl 5-chloro-1-methyl-3-sulfamoyl-indol-2-carboxylate were added to a solution of 2.3 g (0.1 g-atom) of sodium in 200 ml of anhydrous ethanol. The mixture obtained was refluxed for 1 hour and then cooled in an ice-bath. The precipitate thus formed, the sodium salt of 7-chloro-4-methyl-2H-isothiazolo[4,5-b]indol-3(4H)-one-1,1-dioxide, was filtered off, washed in ethanol and ether, dried and subsequently dissolved in 60 ml of dry dimethylsulfoxide. The solution obtained was reacted with 13 g (0.12 mol) of methyl chloroacetate. The resultant solution was heated for one hour in an oil bath to 125°C, then cooled in an ice-bath and treated with a solution of 50 g of sodium acetate in 250 ml of water. The precipitate thus formed was filtered off, washed with ice-water, ice-cold methanol and ether and dried. Yield: 26.1 g (79% of theory) of methyl 7-chloro-3,4-dihydro-4-methyl-3-oxo-2H-isothiazolo-[4,5-b]indol-2-acetate-1,1-dioxide;
M.p.: 271—272°C.

e) methyl 8 - chloro - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino[5,6 - b]-indol - 3 - carboxylate - 1,1 - dioxide

25 ml of anhydrous tert.butanol were added to a well-stirred suspension of 26 g (76 mmol) of methyl 7-chloro-3,4-dihydro-4-methyl-3-oxo-2H-isothiazolo[4,5-b]-indol-2-acetate-1,1-dioxide and 12.3 g (228 mmol) of sodium methylate in 200 ml of anhydrous toluene, whereupon the temperature increased to about 15°C and the colour of the reaction mixture became orange. After 45 min. of stirring at room temperature, the mixture obtained was heated in an oil bath at 60°C for 1.5 hours. 100 ml of ice-water were then stirred into the cooled mixture and the aqueous phase was separated and acidified to pH 3—4 with hydrochloric acid. The

precipitate thus formed was filtered off and washed with ice-water, ice-cold methanol and ether. Yield: 14.1 g (54% of theory) of methyl 8-chloro-2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino-[5,6-b]indol-3-carboxylate-1,1-dioxide; M.p.: 258°C (decomposition).

f) methyl 8 - chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide

A solution of 1.7 g (42 mmol) of sodium hydroxide in 50 ml of water was added dropwise into a suspension of 13.8 g (40 mmol) of methyl 8-chloro - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino[5,6 - b]indol-3 - carboxylate - 1,1 - dioxide and 17 g (0.12 mol) of methyl iodide in 150 ml of methanol.

After 24 hours of stirring at room temperature the resultant mixture was cooled. The precipitate formed was filtered off and washed with water, ice-cold methanol and ether. Yield: 10.2 g (71.5% of theory) of methyl 8 - chloro - 2,5-dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino - [5,6 - b]indol-3 - carboxylate - 1,1 - dioxide; M.p.: 184°C (decomposition).

Example 19.

8 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methyl - thiazol-2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 18 from methyl 8 - chloro - 2,5 - dihydro-2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxylate-1,1 - dioxide and 2 - amino - 4 - methyl - thiazole in an 81% yield.

$C_{17}H_{15}ClN_4O_4S_2$ (438.92)

Calc.: C 46.52 H 3.44 Cl 8.08 N 12.77 S 14.61

Found: 46.40 3.58 8.01 12.90 14.55

Example 20.

8 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 2 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 18 from methyl 8 - chloro-2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino - [5,6 - b]indol-3 - carboxylate - 1,1 - dioxide and 2 - aminopyridine in a 72% yield: M.p.: 245°C (decomposition).

Example 21.

8 - chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 18 from methyl 8 - chloro - 2,5 - dihydro-2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxylate - 1,1-dioxide and aniline in a 77% yield; M.p.: 285°C (decomposition).

Example 22.

Analogously to Example 18, the following compounds were prepared from 2 -aminothiazole and methyl 2,5 - dihydro - 2,5 - dimethyl - 8 - fluoro - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide; methyl 8 - bromo - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide; methyl 2,5 -dihydro - 2,5 - dimethyl-6 - fluoro - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1-dioxide; methyl 7 - chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide; and methyl 9 - chloro-2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]-indol - 3 - carboxylate - 1,1 - dioxide respectively:

22.1 2,5 - Dihydro - 2,5 - dimethyl - 8 - fluoro - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; Yield: 81% of theory.

22.2 8 - Bromo - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; Yield: 76% of theory.

22.3 2,5 - Dihydro - 2,5 - dimethyl - 6 - fluoro - 4 - hydroxy - N - (thiazol - 2 - yl)-

1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; Yield: 87% of theory.

22.4 7 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)- 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; Yield 68% of theory.

22.5 9 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)- 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; Yield: 83% of theory.

The respective starting materials may be obtained from methyl 5-fluoro-indol-2-carboxylate, ethyl 5-bromo-indol-2-carboxylate, ethyl 7-fluoro-indol-2-carboxylate, ethyl 6-chloro-indol-2-carboxylate and ethyl 4-chloro-indol-2-carboxylate respectively by sequential reaction with methyl iodide analogously to Example 18a, followed by reaction with thionyl chloride and ammonia analogously to Example 18b, then with potassium permanganate analogously to Example 18c, then with sodium methylate and methyl chloroacetate analogously to Example 18d and finally with sodium methylate analogously to Example 18e and with methyl iodide analogously to Example 18f.

Example 23.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - (thiazol-2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

5.3 g (0.015 mol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate, 1.6 g (0.016 mol) of 2-aminothiazole and 50 mg of tri - n - butyl borate were refluxed together for 5.5 hours in 500 ml of dry xylene. The methanol formed was separated off using a 4Å molecular sieve in a Soxhlet apparatus. By filtration of the hot resultant mixture, 2.4 g of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - (thiazol - 2-yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide followed, after cooling, standing overnight and subsequent filtration, by a further by 2.2 g. Yield: 73% of theory; M.p.: 249°C (decomposition).

The starting material may be obtained by the following steps:

a) methyl 5 - methoxy - 1 - methyl - indol - 2 - carboxylate

50 g (0.24 mol) of methyl 5 - methoxy - indol - 2 - carboxylate were reacted with 11 g (0.25 mol) of a 55% dispersion of sodium hydride in oil and 42.6 g (0.3 mol) of methyl iodide analogously to Example 18a. The resultant product was recrystallized from methanol. Yield: 47.7 g (90% of theory) of methyl 5 - methoxy-1 - methyl - indol - 2 - carboxylate; M.p.: 129.5—130°C.

b) methyl 3 - aminosulfinyl - 5 - methoxy - 1 - methyl - indol - 2 - carboxylate

Onto 30 g (0.137 mol) of methyl 5-methoxy-1-methyl-indol-2-carboxylate, in a 500 ml flask provided with a gas outlet tube, were poured 70 ml of thionyl chloride with steady stirring. A spontaneous vigorous development of gas occured. After 5 min. of stirring at room temperature, 50 ml of ether were added thereto. After another 30 min. the precipitate formed was filtered off and washed with ether. 36 g of methyl 3-chloro-sulfinyl-5-methoxy-1-methyl-indol-2-carboxylate were obtained (M.p.: under decomposition at 90°C). Another 4.8 g of product were isolated from the filtrate after evaporation *in vacuo*, suspending of the residue in a little ether and filtration of the suspension obtained. The chlorosulfinyl compound thus formed was immediately added to a solution of 100 ml of condensed ammonia in 400 ml of dry ether at –60°C. Subsequent reaction and reprocessing was performed analogously to Example 18b. 30.5 g of methyl 3-amino-sulfinyl-5-methoxy-1-methyl-indol-2-carboxylate were obtained (79% of theory). M.p.: 149—150°C.

c) methyl 5 - methoxy - 1 - methyl - 3 - sulfamoyl - indol - 2 - carboxylate and 7 - methoxy - 4 - methyl - 2H - isothiozole[4,5 - b]indol - 3 - (4H) - one - 1,1 - dioxide

A suspension of 40.8 g (0.145 mol) of methyl 3 - aminosulfinyl - 5 - methoxy - 1-methyl - indol - 2 - carboxylate in 3 l of acetone was reacted with 17.4 g (0.11 mol) of potassium permanganate in 350 ml of water and subsequently processed analogously to Example 18c. 33.7 g (78% of theory) of methyl 5 - methoxy - 1 - methyl - 3 - sulfamoyl - indol - 2 - carboxylate (M.p.: 190°C) and 7.4 g (19% of theory) of 7 - methoxy - 4 - methyl - 2H - isothiazolo - [4,5 - b]-

indol - 3 - (4H) - one - 1,1 - dioxide (M.p.: above 290°C decomposition), were obtained.

d) methyl 3,4 - dihydro - 7 - methoxy - 4 - methyl - 3 - oxo - 2H - isothiazolo-[4,5 - b]indol - 2 - acetate - 1,1 - dioxide

33.4 g (0.112 mol) of methyl 5 - methoxy - 1 - methyl - 3 - sulfamoyl - indol - 2-carboxylate were reacted with sodium methylate in ethanol to form the sodium salt of 7 - methoxy - 4 - methyl - 2H - isothiazolo[4,5 - b]indol - 3 - (4H) - one - 1,1-dioxide which was subsequently converted to methyl 3,4 - dihydro - 7 - methoxy - 4-methyl - 3 - oxo - 2H - isothiazolo - [4,5 - b]indol - 2 - acetate - 1,1 - dioxide analogously to Example 18d; Yield: 34.5 g (91% of theory): M.p.: 205°C.

e) methyl 2,5 - dihydro - 4 - hydroxy - 8 methoxy - 5 - methyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide

35.1 g (0.104 mol) of methyl 3,4 - dihydro - 7 - methoxy - 4 - methyl - 3 - oxo-2H - isothiazolo[4,5 - b]indol - 2 - acetate - 1,1 - dioxide were reacted, analogously to Example 18e, with sodium methylate in toluene/tert. butanol to form 20.6 (59% of theory) of methyl 2,5 - dihydro - 4 - hydroxy - 8 - methoxy-5 - methyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide;
M.p.: 225—226°C.

f) methyl 2,5-dihydro-2,5-dimethyl-4-hydroxy-8-methoxy-1,2-thiazino[5,6-b]-indol-3-carboxylate-1,1-dioxide

20.4 g (60 mmol) of methyl 2,5 - dihydro - 4 - hydroxy - 8 - methoxy - 5 - methyl-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide were reacted analogously to Example 18f with a sodium hydroxide solution and methyl iodide in methanol to yield 17.9 g (85% of theory) of methyl 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 8 - methoxy - 1,2 - thiazino[5,6- b] - indol - 3 - carboxylate-1,1 - dioxide;
M.p.: 200—201°C.

Example 24.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - (pyrid - 2 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

2.1 g (6 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-8 - methoxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.66 g (7 mmol) of 2 - aminopyridine were refluxed together in 250 ml of xylene for 5.5 hours. The mixture obtained was cooled and filtered. 1.9 g (77% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - (pyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide were obtained;
M.p.: 252°C (decomposition).

Example 25.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - phenyl - 1,2 - thiazino-[5,6 - b]indol - carboxamide - 1,1 - dioxide

Produced analogously to Example 23 from methyl 2,5 - dihydro - 2,5-dimethyl - 4 - hydroxy - 8 - methoxy - 1,2 - thiazino - [5,6- b]indol - 3 - carboxylate-1,1 - dioxide and aniline in 78% of yield;
M.p.: 246—247°C (decomposition).

Example 26.

2,5 - Dihydro - 4 - hydroxy - N - (thiazol - 2 - yl) - 2,5,8 - trimethyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.5 g (4.5 mmol) of methyl 2,5 - dihydro - 4 - hydroxy - 2,5,8 - trimethyl - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide, 0.5 g (5 mmol) of 2 - amino-thiazole and 0.1 g of tri - n - butyl borate were refluxed together in 180 ml of xylene for 6 hours. After cooling the resultant mixture the crystals thus formed were filtered off and recrystallized from ethylene chloride/ethanol. Yield: 0.7 g (38% of theory) of 2,5 - dihydro - 4 - hydroxy - N - (thiazol - 2 - yl)-2,5,8 - trimethyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
M.p.: 265°C (decomposition).

$C_{17}H_{16}N_4O_4S_2$ (404.48)

Calc.: C 50.48 H 3.99 N 13.85 S 15.86

Found: 50.30 3.96 13.84 15.75

The starting material may be obtained by the following steps:

a) ethyl 1,5 - dimethyl - indol - 2 - carboxylate

6.6 g (33 mmol) of ethyl 5 - methyl - indol - 2 - carboxylate were reacted, analogously to Example 18a, with 1.6 g of a 55% solution of sodium hydride in oil (36 mmol) and 4.7 g (33 mmol) of methyl iodide in hexamethylphosphoric acid triamide to yield, after recrystallization from ethanol, 4.0 g (56% of theory) of ethyl 1,5 - dimethyl - indol - 2 - carboxylate;
M.p.: 50—52°C.

b) ethyl 3 - aminosulfinyl - 1,5 - dimethyl - indol - 2 - carboxylate

10.0 g (51 mmol) of ethyl 1,5 - dimethyl - indol - 2 - carboxylate were reacted, analogously to Example 18b, with 28 ml of thionyl chloride and the yellow crystallisate thus obtained (ethyl 3 - chlorosulfinyl - 1,5 - dimethyl - indol - 2-carboxylate) was reacted with a solution of ammonia in ether at −70°C to yield 8.8 g (61% of theory) of ethyl 3 - aminosulfinyl - 1,5 - dimethyl - indol - 2-carboxylate;
M.p.: 118°C.

c) ethyl 1,5 - dimethyl - 3 - sulfamoyl - indol - 2 - carboxylate and 4,7 - dimethyl-2H - isothiazolo[4,5 - b]indol - 3(4H) - one - 1,1 - dioxide

8.0 g (29 mmol) of ethyl 3 - aminosulfinyl - 1,5 - dimethyl - indol - 2-carboxylate were reacted, analogously to Example 18c, with 3.0 g (19 mmol) of sodium permanganate to yield 5.9 g (70% of theory) of ethyl 1,5 - dimethyl - 3 - sulfamoyl - indol - 2 - carboxylate;
M.p.: 148°C,
and
2.0 g (28% of theory) of 4,7 - dimethyl - 2H - isothiazolo - [4,5 - b]indol - 3(2H)-one-1,1 - dioxide;
M.p.: 295°C (decomposition).

By heating with an equivalent of sodium methylate in ethanol and subsequent acidification, the ethyl 1,5 - dimethyl - 3 - sulfamoyl - indol - 2 - carboxylate can be converted into 4,7 - dimethyl - 2H - isothiazolo[4,5 - b]indol - 3(2H)-one - 1,1 - dioxide.

d) methyl 3,4 - dihydro - 4,7 - dimethyl - 3 - oxo - 2H - iso - thiazolo[4,5 - b]indol-2 - acetate - 1,1 - dioxide

3.0 g (27.5 mmol) of methyl chloroacetate were added to a solution of 1.35 g (25 mmol) of sodium methylate and 6.9 g (23 mmol) of 4,7 - dimethyl - 2H - isothiazolo[4,5 - b]indol - 3(2H) - one - 1,1 - dioxide in 15 ml of anhydrous dimethylsulfoxide. The resultant mixture was then heated for one hour to 130°C and, after cooling, stirred into a solution of 2.5 g of sodium acetate in 40 ml of water. The precipitate thus formed was isolated, washed with ice-water, dried and recrystallized to yield 3.6 g (48% of theory) of methyl 3,4 - dihydro - 4,7 - dimethyl-3 - oxo - 2H - isothiazolo - [4,5 - b]indol - 2 - acetate - 1,1 - dioxide;
M.p.: 248°C.

e) methyl 2,5 - dihydro - 5,8 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]-indol - 3 - carboxylate - 1,1 - dioxide

4.0 g of methyl 3,4 - dihydro - 4,7 - dimethyl - 3 - oxo - 2H - isothiazolo-[4,5 - b]indol - 2 - acetate - 1,1 - dioxide were reacted, analogously to Example 18e, with 2.0 g of sodium methylate in toluene/tert. butanol to yield, after further processing and recrystallization from ethylene chloride/methanol, 2.0 g (50% of theory) of methyl 2,5 - dihydro - 5,8 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide;
M.p.: 260°C (decomposition).

f) methyl 2,5 - dihydro - 4 - hydroxy - 2,5,8 - trimethyl - 1,2 - thiazino[5,6 - b]indol-3 - carboxylate - 1,1 - dioxide

1.7 g of methyl 2,5 - dihydro - 5,8 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide were reacted, analogously to Example 18f, with 5.3 ml of 1 N sodium hydroxide solution and 2.6 g of methyl iodide in 20 ml of methanol to yield 1.5 g (84% of theory) of methyl 2,5 - dihydro - 4-hydroxy - 2,5,8 - trimethyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1-dioxide;
M.p.: 144—145°C.

Example 27.

2,5 - Dihydro - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl) - 2,5,8 - trimethyl -1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Methyl 2,5 - dihydro - 4 - hydroxy - 2,5,8 - trimethyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide was reacted with 2 - amino - 4 - methyl-thiazole, analogously to Example 26, to give 2,5 - dihydro - 4 - hydroxy - N - (4-methyl - thiazol - 2 - yl) - 2,5,8 - trimethyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 52% of theory.

Example 28.

Analogously to Example 26, the following compounds were produced from 2 - aminothiazole and methyl 8 - ethyl - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 - b] - indol - 3 - carboxylate - 1,1 - dioxide; methyl 2,5 - dihydro-2,5 - dimethyl - 4 - hydroxy - 7 - trifluoromethyl - 1,2 - thiazino - [5,6 - b]indol-3 - carboxylate - 1,1 - dioxide and methyl 2,5 - dihydro - 4 - hydroxy - 2,5,7-trimethyl - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxylate - 1,1 - dioxide respectively:

28.1 8 - Ethyl - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 61% of theory;

28.2 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 7 - trifluoro-methyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 47% of theory;

28.3 2,5 - Dihydro - 4 - hydroxy - N - (thiazol - 2 - yl - 2,5,7 - trimethyl - 1,2 - thia-zino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 58% of theory.

The respective starting materials may be obtained from ethyl 5-ethyl-indol-2-carboxylate; ethyl 6-tri-fluoromethyl-indol-2-carboxylate; and ethyl 6-methyl-indol-2-carboxylate respectively by sequential reactions with methyl iodide analogously to Example 26a, with thionyl chloride and ammonia analogously to Example 26b, with potassium permanganate analogously to Example 26c, with sodium methylate and methyl chloroacetate analogously to Example 26d and finally by treatment with sodium methylate analogously to Example 26e and with methyl iodide analogously to Example 26f.

Example 29.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino - [5,6 - b]-indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 9 from methyl 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and aniline in toluene;
M.p.: 269—270°C (decomposition);

$C_{19}H_{17}N_3O_4S$ (383.43)

Calc.: C 59.52 H 44.47 N 10.96 S 8.36

Found: 59.50 44.56 10.71 8.37

Example 30.

2,5 - Dihydro - 2,5 - dimethyl - N - (4 - fluorophenyl) - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to example 9 from n-butyl 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 4-fluoroaniline in xylene;
M.p.: 271—272°C (decomp.); Yield: 68% of theory;

$C_{19}H_{16}FN_3O_4S$ (401.42)

Calc.: C 56.86 H 4.02 N 10.47 S 7.99

Found: 56.90 3.97 10.78 8.31

The starting material n-butyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide,
M.p.: 143—145°C from xylene;

$C_{17}H_{20}N_2O_5S$ (364.43)

Calc.: C 56.02 H 5.53 N 7.69 S 8.80

Found: 55.90 5.53 7.69 9.00

was produced from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and n-butanol in xylene;
Yield: 73% of theory.

Example 31.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 2 from benzyl 2,4 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 2 - amino - 4 - methyl - thiazole in xylene;
M.p.: 270°C (decomp.);
Yield: 67% of theory;

$C_{17}H_{16}N_4O_4S$ (404.47)

Calc.: C 50.48 H 3.99 N 13.85 S 15.85

Found: 50.50 3.81 13.88 15.61

The starting material benzyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide,
M.p.: 208—209°C;

$C_{20}H_{18}N_2O_5S$ (398.45)

Calc.: C 60.29 H 4.55 N 7.03 S 8.05

Found: 60.10 4.58 6.93 7.94

was produced from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and benzyl alcohol in xylene;
Yield: 84% of theory.

Example 32.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

0.32 g (1.0 mmol) of phenyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.12 g (1.2 mmol) of 2 - aminothiazole were refluxed together in 30 ml of xylene for 1 hour. After cooling and being allowed to stand overnight, the crystals thus formed were

filtered off with suction and washed in ether.
Yield: 0.35 g (90% of theory);
M.p.: 260—261°C (decomposition).

$C_{16}H_{14}N_4O_4S_2$ (390.44)

Calc.: C 49.22 H 3.55 N 14.42 S 16.43

Found: 49.30 3.51 14.57 16.31

The starting material phenyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide,
M.p.,: 262—264°C (decomposition);

$C_{19}H_{16}N_2O_5S$ (384.42)

Calc.: C 59.36 H 4.20 N 7.29 S 8.34

Found: 59.30 4.15 7.23 8.45

was produced from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and an excess of phenol in xylene;
Yield: 51% of theory.

Example 33.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.3 g (9 mmol) of methyl iodide were added to a solution of 1.0 g (2.7 mmol) of 2,5 - dihydro - 4 - hydroxy - 5 - methyl - N - phenyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide in 30 ml of methanol and 2.7 ml of a 1N sodium hydroxide solution. The resultant mixture was stirred for 6 hours at room temperature and then neutralised. The precipitate thus formed was filtered off, washed with water and recrystallized from xylene. Yield: 750 mg (73% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
M.p.: 269—270°C (decomposition);

$C_{18}H_{17}N_3O_4S$ (383.43)

Calc.: C 59.52 H 4.47 N 10.96 S 8.36

Found: 59.50 4.58 10.81 8.44

Example 34.

Analogously to Example 33 the following compounds were obtained from methyl iodide and 2,5 - dihydro - 4 - hydroxy - 5 - methyl - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide; 2,5 - dihydro - 4-hydroxy - 5 - methyl - N - (4 - methylthiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]-indol - 3 - carboxamide - 1,1 - dioxide; 2,5 - dihydro - N - (4,5 - dimethyl-thiazol - 2 - yl) - 4 - hydroxy - 5 - methyl - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; 2,5 - dihydro - 4 - hydroxy - 5 - methyl - N - (pyrid-2 - yl) - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide; and 2,5-dihydro - 4 - hydroxy - 5 - methyl - N - (6 - methylpyrid - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide respectively:

34.1 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide; Yield: 18% of theory; M.p.: 260—261°C (decomposition);

34.2 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methyl - thiazol - 2 -yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 27% of theory;
M.p.: 270°C (decomposition);

34.3 2,5 - Dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol - 2 - yl) - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 22% of theory:
M.p.: 265°C (decomposition);

34.4 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 31% of theory;
M.p.: 232—233°C (decomposition);

34.5 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methyl - pyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 25% of theory:
M.p.: 229°C (decomposition);

The same results with the same yields were attained by reaction with methyl bromide instead of methyl iodide.

Example 35.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

A solution of 1.0 g (3.7 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino-[5,6 - b]indol - 4(3H) - one - 1,1 - dioxide and 0.44 ml (4.0 mmol) of phenyl isocyanate in 20 ml of dimethylformamide was added, cooling with ice, to a suspension of 230 mg of a 55% sodium hydride in oil dispersion (5.0 mmol) in 15 ml of dimethylformamide. The mixture obtained was stirred for 30 min. in an ice bath and subsequently for 4 hours at room temperature then poured, whilst stirring into 100 ml of 3N hydrochloric acid. The precipitate thus formed was filtered off, washed with water, dried and recrystallized from xylene to yield 340 mg (27% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino[5,6-b]indol - 3 - carboxamide - 1,1 - dioxide;
M.p.: 269—270°C (decomposition).

$C_{19}H_{17}N_3O_4S$ (383.43)

Calc.: C 59.52 H 4.47 N 10.96 S 8.36

Found: 59.40 4.57 10.99 8.31

The starting material may be prepared via the following steps:

a) 2 - acetonyl - 4 - methyl - 2H - isothiazolo[4,5 - b]indol - 3 - (4H) - one - 1,1-dioxide

50 ml of dimethylsulfoxide were added, with cooling, to a mixture of 2.4 g (45 mmol) of sodium methylate and 10 g (42 mmol) of 4 - methyl - 2H - isothiazolo-[4,5 - b]indol - 3 - (4H) - one - 1,1 - dioxide. After one hour of stirring at room temperature, 4.6 g (50 mmol) of chloroacetone were added thereto. The mixture obtained was heated for 2.5 hours in an oil bath at 125°C and, after cooling, a solution of 15 g of sodium acetate in 400 ml of water was added thereto. The precipitate thus formed was filtered off, washed with water, ice-cold methanol and ether and dried. Yield: 8.3 g (68% of theory) of 2 - acetonyl - 4 - methyl - 2H - isothiazolo[4,5 - b]indol - 3 (4H) - one - 1,1 - dioxide; M.p.: 188—189°C (from ethylene chloride).

b) 3 - acetyl - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino[5,6 - b]indol-1,1 - dioxide

10 g (34 mmol) of 1 - acetonyl - 4 - methyl - 2H - isothiazolo[4,5 - b]indol-3(4H) - one - 1,1 - dioxide were added to a methanolic sodium methylate solution [1.6 g of sodium (0.07 g-atoms) in 60 ml of anhydrous methanol]. After half an hour of stirring at room temperature, the mixture obtained was heated for 45 min. in an oil bath at 60°C, then cooled in an ice bath and acidified with 1N hydrochloric acid to a pH of 3—4. The precipitate thus formed was filtered off, washed with ice-water, dried and recrystallized from ethylene chloride: 6.4 g (64% of theory) of 3-acetyl-2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino[5,6-b]indol-1,1-dioxide were obtained.

M.p.: 210—211°C;

$C_{13}H_{12}N_2O_4S$ (292.32)

Calc.: C 53.42 H 4.14 N 9.58 S 10.97

Found: 53.60 4.07 9.58 10.63

c) 2,5 - dihydro - 5 - methyl - 1,2 - thiazino[5,6 - b]indol - 4(3H) - one - 1,1 - dioxide ethylene ketal

6.2 g (21.2 mmol) of 3 - acetyl - 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2-thiazino[5,6 - b]indol - 1,1 - dioxide, 12.4 g (0.2 mol) of freshly distilled glycol and 0.5 g of *p*-toluenesulfonic acid were refluxed together in 300 ml of benzene for 120 hours using a water separator. After addition of a further 300 ml of benzene, the mixture obtained was washed with sodium hydrogen carbonate solution until neutral and then treated with active carbon, dried over magnesium sulfate and evaporated to a volume of about 30 ml. 2.9 g (47% of theory) of 2,5 - dihydro - 5 - methyl - 1,2 - thiazino[5,6 - b]indol - 4(3H) - one - 1,1 - dioxide ethylene ketal crystallized out;
M.p.: 205—206°C (from benzene).

d) 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino[5,6 - b]indol - 4(3H) - one - 1,1-dioxide ethylene ketal

2.7 g (9.2 mmol) of 2,5 - dihydro - 5 - methyl - 1,2 - thiazino[5,6 - b]indol-4(3H) - one - 1,1 - dioxide ethylene ketal and 1.92 g (13.5 mmol) of methyl iodide, in 30 ml of isopropanol, were suspended in 10 ml of water and 9.7 ml of a 1N sodium hydroxide solution (9.7 mmol) were added thereto. After stirring for 24 hours at room temperature, the precipitate thus formed was filtered off with suction, washed with water and ice-cold isopropanol and recrystallized from ethanol. Yield: 2.4 g (88% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino-[5,6 - b]indol - 4(3H) - one - 1,1 - dioxide ethylene ketal;
M.p.: 184°C.

e) 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino[5,6 - b]indol - 4(3H) - one - 1,1-dioxide

2.2 g (7.4 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino[5,6 - b]indol-4(3H) - one - 1,1 - dioxide ethylene ketal were refluxed for one hour in a mixture of 60 ml of 9% hydrochloric acid and 60 ml of methanol. The mixture obtained was evaporated *in vacuo*. The residue was dissolved in methylene chloride and the solution obtained was washed with water, dried and evaporated. The residue was recrystallized from ethanol. 1.6 g (82% of theory) of 2,5 - dihydro - 2,5 - dimethyl-1,2 - thiazino[5,6 - b]indol - 4(3H) - one - 1,1 - dioxide were obtained;
M.p.: 180°C; ^{1}H—NMR ($CDCl_3$): δ = 8.0 (m,l) and 7.4 (m,3; arom. H) 4.15 (s, 2, CH_2); 4.06 (s, 3, 5—CH_3); 3.00 (s, 3, 2—CH_3).

$C_{12}H_{12}N_2O_3S$ (264.31)

Calc.: C 54.53 H 4.57 N 10.60 S 12.13

Found: 54.30 4.57 10.65 11.85

Example 36.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 -yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1 g (2.6 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide was refluxed for 48 hours with 800 mg (8 mmol) of 2 - aminothiazole, 0.1 g of tri - n - butyl borate and 0.1 g of *p*-toluenesulfonic acid in 250 ml of xylene. After cooling, the mixture obtained was filtered. The precipitate thus isolated was directly used in the subsequent column chromatographic separation. The filtrate was shaken with 3 N aqueous hydrochloric acid, washed, dried and evaporated. The combined solid fractions were purified by column chromatograph "Merck"[Registered Trade Mark]-Kieselgel 60, grain size: 0.2—0.5 mm; eluant: chloroform/ethanol, 9:1). Yield: 0.35 g (34% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-

N - (thiazol - 2 - yl) - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide; M.p.: 260—261°C (decomposition).

$C_{16}H_{14}N_4O_4S_2$ (390.44)

Calc.: C 49.22 H 3.55 N 14.42 S 16.43

Found: 49.00 3.61 14.30 16.41

Example 37.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 36 from 2,5 - dihydro - 2,5 - dimethyl - 4-hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and 2 - amino-thiazole in a 46% yield:
M.p.: 260—261°C (decomposition).

The starting material may be prepared according to the following method:

a) 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino[5,6 - b] - indol-3 - carboxamide - 1,1 - dioxide

3 g (10.2 mmol) of methyl 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino-[5,6 b]indol - 3 - carboxylate - 1,1 - dioxide were mixed with 150 ml of concentrated aqueous ammonia and the mixture obtained was stirred for 12 hours at room temperature. The mixture was then evaporated *in vacuo* and the residue was treated with ice-water. The precipitate thus formed was filtered off with suction, washed with a small amount of ice-water and recrystallized several times from glacial acetic acid. Yield: 20 g (70% of theory) of 2,5 - dihydro - 4 - hydroxy-5 - methyl - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide.

$C_{12}H_{11}N_3O_4S$ (293.31)

Calc.: C 49.14 H 3.78 N 14.33 S 10.93

Found: 49.30 3.63 14.17 10.81

b) 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino - [5,6- b]indol-3 - carboxamide - 1,1 - dioxide

1.5 g (5.1 mmol) of 2,5 - dihydro - 4 - hydroxy - 5 - methyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and 0.7 g (5 mmol of methyl iodide were mixed with a solution of 0.27 g (5 mmol) of sodium methylate in 20 ml of dimethylformamide. The resultant mixture was stirred for 20 hours at room temperature and then was weakly acidified with 1N hydrochloric acid. The precipitate thus formed was filtered off with suction and recrystallized from ethylene chloride/ethanol.
Yield: 1.05 g (67% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxyl - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide.

$C_{13}H_{13}N_3O_4S$ (307.34)

Calc.: C 50.81 H 4.26 N 13.67 S 10.43

Found: 50.80 4.25 13.63 10.37

Example 38.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 36 from N - (n - butyl) - 2,5 - dihydro - 2,5-dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide and 2 - aminothiazole in a 37% yield; M.p.: 260—261°C (decomp).

The starting material N - (n - butyl) - 2,5 - dihydro - 2,5 - dimethyl - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide was obtained analogously to Example 35 from 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino[5,6 - b]indol - 4(3H)-one - 1,1 - dioxide and n - butyl isocyanate in a 42% yield.

Analogously the following compounds were obtained from N - (n - butyl) - 2,5-

dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide-1,1 - dioxide:

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methyl - thiazol - 2 - yl)-1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide,
Yield: 33% of theory; M.p.: 270°C (decomposition);

2,5 - Dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol - 2 - yl) - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide,
Yield: 37% of theory; M.p.: 265°C (decomposition);

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide,
Yield: 30% of theory; M.p.: 232—233°C (decomposition);

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methyl - pyrid - 2 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide,
Yield: 28% of theory; M.p.: 229°C (decomposition).

Example 39.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - phenyl - 1,2 - thiazino - [5,6 - b]-indol - 3 - carboxamide - 1,1 - dioxide

0.19 g (2 mmol) of aniline in 5 ml of dry tetrahydrofuran were added dropwise at –40°C to a solution of 2,5 - dihydro - 2,5 - dimethyl - 4 - (pyrrolidin - 1 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - chlorocarbonyl - 1,1 - dioxide in tetrahydrofuran (obtained by reaction of 0.32 g (1 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 4-(pyrrolidin - 1 - yl) - 1,2 - thiazino[5,6 - b]indol - 1,1 - dioxide with 0.125 g (1.25 mmol) of phosgene and 0.125 g (1.25 mmol) of triethylamine in 10 ml of anhydrous tetrahydrofuran). The resultant mixture was allowed to warm over 6 hours to room temperature and was subsequently stirred for 24 hours. Ice-water was then added thereto and the mixture obtained was extracted twice with methylene chloride. The organic phase was washed twice with water, dried over sodium sulfate and evaporated *in vacuo*. The residue, crude 2,5 - dihydro - 2,5 - dimethyl - N - phenyl-4 - (pyrrolidin - 1 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide, was dissolved in 6 ml of glacial acetic acid and the solution obtained was mixed with 2 ml of 2 N hydrochloric acid. The resultant mixture was warmed to 100°C for 15 min. and then, after cooling, 50 ml of ice-water were added thereto. The precipitate thus formed was filtered off, dried and crystallised from xylene.
Yield: 185 mg (48% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-N - phenyl - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide;
M.p.: 269—270°C (decomposition).

$C_{19}H_{17}N_3O_4S$ (383.43)

Calc.: C 59.92 H 4.47 N 10.96 S 8.36

Found: 59.80 4.52 10.90 8.49

Synthesis of the starting material may be performed as follows:

a) 2,5 - dihydro - 2,5 - dimethyl - 4 - (pyrrolidin - 1 - yl) - 1,2 - thiazino-[5,6 - b]indol - 1,1 - dioxide

2.64 g (10 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 1,2 - thiazino[5,6 - b]indol-4(3H) - one - 1,1 - dioxide were heated with 1.0 g (14 mmol) of freshly distilled pyrrolidine and 0.1 g of *p* - toluenesulfonic acid in 200 ml of benzene for 96 hours using a water separator. After each 24 hours, equal quantities of pyrrolidine and *p*-toluene sulfonic acid were added to the mixture. The resultant mixture was cooled then mixed with ether and washed until neutral. The organic phase was separated, dried and evaporated. The residue was purified by recrystallization from ethanol. Yield: 1.4 g (44% of theory) of 2,5 - dihydro - 2,5 - dimethyl-4 - (pyrrolidin - 1 - yl) - 1,2 - thiazino[5,6 - b]indol - 1,1 - dioxide;
^{1}H—NMR ($CDCl_3$): δ = 8.00 (m, 1) and 7.4 (m, 3; arom. H); 6.05 (s, 1, 3—H); 4.10 (s, 3, 6—CH_3); 3.27 (s, 3, 2—CH_3); 2.93 (m, 4, N—$(CH_2)_2$); 1.95 (m, 4, —$(CH_2)_2$—).

$C_{16}H_{19}N_3O_2S$ (317.42)

Calc.: C 60.54 H 6.03 N 13.24 S 10.10

Found: 60.50 6.18 13.31 10.17

b) 2,5 - dihydro - 2,5 - dimethyl - 4 - (pyrrolidin - 1 - yl) - 1,2 - thiazino[5,6 - b]-indol - 3 - chlorocarbonyl - 1,1 - dioxide

A solution of 0.32 g (1 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 4 - (pyrrolidin-1 - yl) - 1,2 - thiazino[5,6 - b]indol - 1,1 - dioxide and 0.125 g (1.25 mmol) of triethylamine in 8 ml of anhydrous tetrahydrofuran, cooled to –40°C, was added to a solution, cooled to –40°C, of 0.125 g (1.25 mmol) of phosgene (0.65 ml of a 20% solution in toluene) in 2 ml of anhydrous tetrahydrofuran. The temperature of the mixture obtained was allowed to rise to room temperature over one hour. The mixture was then allowed to stand for a further 2 hours at room temperature. The enaminic acid chloride obtained in this way, in the form of a tetrahydrofuran solution, was then used directly for further reaction.

Example 40.

Analogously to Example 39 the following compounds were prepared from 2,5-dihydro - 2,5 - dimethyl - 4 - (pyrrolid - 1 - yl) - 1,2 - thiazino[5,6 - b]indol-3 - chlorocarbonyl - 1,1 - dioxide and 2 - amino - thiazole, 2 - amino - 4 - methylthiazole, 2 - amino - 4,5 - dimethylthiazole, 2 - amino - pyridine and 2 - amino - 6-methylpyridine respectively:

40.1 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 40% of theory; M.p.: 260—261°C (decomposition);

40.2 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl)-1,2 - thiazino[5, 6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 36% of theory; M.p.: 270°C (decomposition);

40.3 2,5 - Dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol - 2 - yl)-4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 33% of theory; M.p.: 265°C (decomposition);

40.4 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 2 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 38% of theory; M.p.: 232—233°C (decomposition);

40.5 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methylpyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 28% of theory; M.p.: 229°C (decomposition).

Example 41.

Sodium salt of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

0.064 mg (1 mmol) of sodium methylate were added to a suspension of 0.39 g (1 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide in 50 ml of methanol. The mixture obtained was then stirred for 24 hours at room temperature and subsequently evaporated under high vacuum and treated with isopropanol/ether. The crystals obtained were filtered off with suction;
Yield: 0.31 g (75% of theory) of the sodium salt;
M.p.: 265°C (decomposition).

Example 42.

Cyclohexylamine salt of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1-dioxide

0.1 g (1 mmol) of cyclohexylamine were added to a suspension of 0.4 g (1 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methylthiazol - 2 - yl) - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide in 50 ml of methanol. The solution obtained was stirred at room temperature for 24

hours and then evaporated *in vacuo*. The residue was treated with acetone/ether and the resultant solid was filtered off with suction and washed with ether. Yield: 0.36 g (72% of theory) of cyclohexylamine salt.
M.p.: 178°C (decomposition).

$C_{23}H_{29}N_5O_4S_2$ (503.66)

Calc.: C 54.85 H 5.80 N 13.91 S 12.73

Found: 54.60 6.02 13.82 12.91

Example 43.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (isothiazol - 3 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.0 g (3.1 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.33 g (3.3 mmol) of 3 - amino-isothiazole were refluxed together in 100 ml of xylene for 6 hours. The mixture obtained was evaporated to a volume of about 10 ml and the crystals obtained were filtered off with suction. Yield: 0.9 g (74% of theory) of 2,5 - dihydro-2,5 - dimethyl - 4 - hydroxy - N - (isothiazol - 3 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide.

$C_{16}H_{14}N_4O_4S_2$ (390.44)

Calc.: C 49.22 H 3.55 N 14.42 S 16.43

Found: 49.30 3.71 14.30 16.18

Example 44.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (5 - methylisothiazol - 3 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Produced analogously to Example 43 from methyl 2,5 - dihydro -2,5 - dimethyl-4 - hydroxy - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxylate - 1,1 - dioxide and 2-amino - 5 - methyl - isothiazole with a yield of 82% of theory.

Example 45.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (3 - hydroxypyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.0 g (3.1 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.36 g (3.3 mmol) of 2 - amino - 3 - hydroxy - pyridine were refluxed together for 6.5 hours in 150 ml of xylene. The hot resultant mixture was filtered and the crystals obtained were washed and dried. Yield: 1.2 g (97% of theory) of 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - N - (3 - hydroxypyrid - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
M.p.: 255°C (decomposition).

$C_{18}H_{16}N_4O_5S$ (400.42)

Calc.: C 53.99 H 4.03 N 13.99 S 8.01

Found: 53.86 4.92 13.86 7.90

Example 46.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrimidin - 4 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Analogously to Example 45, 0.7 g (2.1 mmol of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxyl - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.24 g (2.5 mmol) of 4 - aminopyrimidine were reacted together. 0.7 g (86% of theory) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrimidin - 4 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide were obtained;
M.p.: 255°C (decomposition).

Example 47.

Analogously to Example 45 the following compounds were prepared from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3-carboxylate - 1,1 - dioxide and 3 - aminopyridine, 4 - aminopyridine and aminopyrazine respectively:

2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 3 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 76% of theory;

2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (pyrid - 4 - yl) - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 83% of theory;

2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - pyrazinyl - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 91% of theory; M.p.: 252°C (decomp).

Example 48.

N - (Benzimidazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

1.0 g (3.1 mmol) of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and 0.41 g (3.1 mmol) of 2 - aminobenzimidazole, in 180 ml of xylene, were refluxed together for 6 hours. The crystals formed in the hot solution were filtered off with suction, washed and dried. Yield: 1.1 g (84% of theory) of N - (benzimidazol - 2 - yl) - 2,5 - dihydro-2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1-dioxide;
M.p.: > 305°C.

Example 49.

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methyloxazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

3.0 g (9.1 mmol) of methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxylate - 1,1 - dioxide and 0.98 g (10 mmol) of 2 - amino - 4 - methyl - oxazole were refluxed together for 4 hours in 250 ml of xylene. On subsequent cooling the crude product crystallized out. Recrystallization from ethanol yielded 0.7 g (20% of theory) of 2,5 - dihydro - 2,5 - dimethyl-4 - hydroxy - N - (4 - methyloxazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol-3 - carboxamide - 1,1 - dioxide;
M.p.: 128°C.

$C_{17}H_{16}N_4O_5S$ (388.42)

Calc.: C 52.57 H 4.15 N 14.43 S 8.26

Found: 52.80 4.20 14.20 8.45

Example 50.

Analogously to Example 49 the following compounds were prepared from methyl 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3-carboxylate - 1,1 - dioxide and 2 - aminooxazole, 2 - amino - 5 - methyl - oxazole and 2 - aminobenzoxazole respectively:

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (oxazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 26% of theory;

2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (5 - methyl - oxazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 36% of theory;

N - (benzisoxazol - 2 - yl) - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide;
Yield: 56% of theory; M.p.: 246°C (decomposition).

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Example I.

Tablets containing 25 mg of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-N - (thiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1-dioxide

Composition:

1 tablet contains	
active ingredient	25.0 mg
corn starch	97.0 mg
polyvinylpyrrolidone	175.0 mg
magnesium stearate	3.0 mg
	300.0 mg

Method of Preparation:

A mixture of the active ingredient with the corn starch is granulated in a 14% aqueous solution of the polyvinylpyrrolidone through a sieve. The granulate obtained is dried at 45°C and again granulated through the above sieve. The resultant granulate is mixed with the magnesium stearate and pressed into tablets.

Weight of tablet	300 mg
Punch	10 mm, flat

Example II.

Coated tablets containing 25 mg of 2,5 - dihydro - 2,5 - dimethyl - 4-hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Composition:

1 core contains	
active ingredient	25.0 mg
corn starch	205.0 mg
gelatine	8.0 mg
talcum	18.0 mg
magnesium stearate	44.0 mg
	300.0 mg

Method of preparation

A mixture of the active ingredient with the corn starch is granulated with a 10% aqueous gelatine solution through a sieve of 1.5 mm/mesh size. The granulate obtained is dried at 45°C and again granulated through the same sieve. The resultant granulate is mixed with the talcum and magnesium stearate and pressed into tablet cores.

Weight of core	300.0 mg
Punch	10 mm, arcuate

The cores are covered with a coating consisting essentially of sugar and talcum. The final coated tablets are polished with bees-wax.

Weight of coated tablet	580 mg

Example III.

Gelatine capsules containing 25 mg of 2,5 - dihydro - 2,5 - dimethyl - 4-hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]- indol - 3 - carboxamide-1,1 - dioxide

Composition:

1 gelatine capsule contains:

active ingredient	25.0 mg
corn starch	365.0 mg
"Aerosil" [registered Trade Mark]	6.0 mg
magnesium stearate	4.0 mg
	400.00 mg

Method of preparation:

The constituents of the composition are intimately mixed and filled into gelatine capsules of size 1.

Capsule ingredient: 400 mg

Example IV.

Suppositories containing 25 mg of 2,5 - dihydro - 2,5 - dimethyl - 4-hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino[5,6 - b] - indol - 3 - carboxamide - 1,1 - dioxide

Composition:

1 suppository contains:

active ingredients	25.0 mmg
suppository mass (e.g. "Witesol" [registered Trade Mark] W 45)	1725.0 mg
	1750.0 mg

Method of preparation:

The highly pulverized active ingredient is stirred by means of an immersion homogeniser into the molten suppository mass cooled to 40°C. The mass is then poured into pre-cooled moulds at 38°C.

Weight of suppository: 1.75 g

Example V.

Suspension containing 5 mg/ml of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 - yl) - 1,2 - thiazino[5,6 - b]indol - 3 - carboxamide-1,1 - dioxide

Composition:

active ingredient	05. g
dioctylsodium sulfosuccinate DONSS	0.02 g
benzoic acid	0.1 g
sodium cyclamate	0.2 g
"Aerosil"	1.0 g
polyvinylpyrrolidone	0.1 g
glycerine	25.0 g
grapefruit aroma	0.1 g
distilled water ad.	100.0 g

Method of preparation:

The DONSS, benzoic acid, sodium cyclamate and polyvinylpyrrolidone are successively dissolved in the water warmed to 70°C. The glycerine and Aerosil are then added. The resultant suspension is cooled down to room temperature and the highly pulverised active ingredient is suspended in this mixture by means of an immersion homogeniser. Subsequently the mixture obtained is aromatised and made up with water to the prescribed volume.

Example VI.

Coated tablets containing 50 mg of 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy-N - (thiazol - 2 - yl) - 1,2 - thiazino - [5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide

Composition:

active ingredient	50.0 mg
lactose	55.0 mg
corn starch	42.0 mg
polyvinylpyrrolidone	2.0 mg
magnesium stearate	1.0 mg
	150.0 mg

Method of preparations:

A mixture consisting of the active ingredient, lactose and corn starch is granulated through a sieve of 1.5 mm mesh size by means of an 8% aqueous solution of the polyvinylpyrrolidone. The granulate is dried at 45°C and again granulated through a sieve of 1.0 mm mesh size. The resultant granulate is mixed with the magnesium stearate and pressed into tablet cores.

Weight of core	150 mg
Punch	8 mm, arcuate

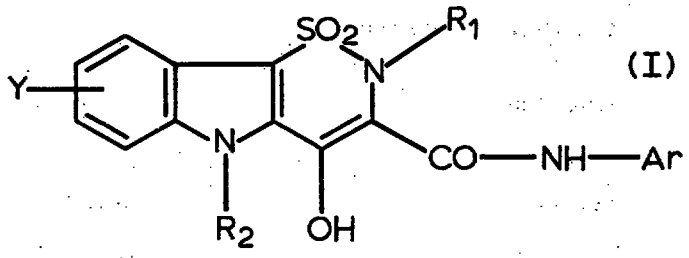
The cores are coated in the usual way with a coating consisting essentially of sugar and talcum. The coated tablets are then polished with bees-wax.

Weight of coated tablet	240 mg

We make no claim herein to compositions containing artificial sweeteners which are contrary to the Artificial sweeteners Regulations presently in force.

Subject to the foregoing disclaimer WHAT WE CLAIM IS:—

1. Compounds of general formula I,



wherein

R_1 represents a hydrogen atom or a methyl or ethyl group;

R_2 represents a methyl or ethyl group;

Y represents a hydrogen, fluorine, chlorine or bromine atom or a methoxy, methyl, ethyl or trifluoromethyl group; and

Ar represents a thiazol - 2 - yl group (optionally substituted by one or two groups selected from methyl and ethyl groups); a 5, 6 - dihydro - 4H - cyclopenta[d]thiazol - 2 - yl, 4,5,6,7 - tetrahydrobenzothiazol - 2 - yl or benzothiazol-2 - yl group; a pyrid - 2 - yl group (optionally substituted by a methyl or hydroxy group); a pyrid - 3 - yl, pyrid - 4 - yl, pyrimidin - 4 yl, pyrazinyl, benzoxazol - 2 - yl or benzimidazol - 2 - yl group; an isothiazol - 3 - yl or oxazol - 2 - yl group (optionally substituted by a methyl group); or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, trifluoromethyl or methoxy group);

and salts thereof with bases.

2. 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 -yl) - 1,2-thiazino-[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with bases.

3. 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (4 - methyl - thiazol - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with bases.

4. 2,5 - Dihydro - 2,5 - dimethyl - N - (4,5 - dimethylthiazol - 2 - yl) - 4 - hydroxy-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with base.

5. 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (6 - methylpyrid - 2 - yl) - 1,2-thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with bases.

6. 8 - Chloro - 2,5 - dihydro - 2,5 - dimethyl - 4 - hydroxy - N - (thiazol - 2 -yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with bases.

7. 2,5 - Dihydro - 2,5 - dimethyl - 4 - hydroxy - 8 - methoxy - N - (pyrid - 2 - yl)-1,2 - thiazino[5,6 - b]indol - 3 - carboxamide - 1,1 - dioxide and salts thereof with bases.

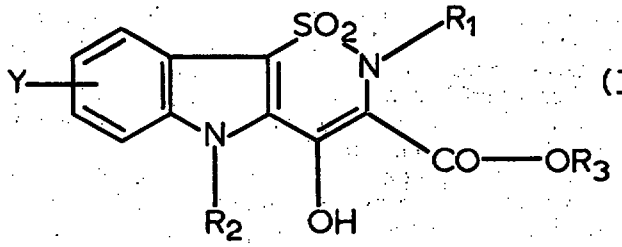
8. Compounds as claimed in any of the preceding claims in the form of physiologically compatible salts with bases.

9. Compounds of general formula I as claimed in claim 1 wherein Ar represents a thiazol - 2 - yl group (optionally substituted by one or two groups selected from methyl and ethyl groups); a 5,6 - dihydro - 4H - cyclopenta[d]thiazol-2 - yl, 4,5,6,7 - tetrahydrobenzothiazol - 2 - yl or benzothiazol - 2 - yl group; a pyrid - 2 - yl group (optionally substituted by a methyl group) or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, trifluoromethyl or methoxy group) and physiologically compatible salts thereof with bases.

10. Compounds as claimed in claim 1, other than those claimed in any of claims 2 to 7, as herein specifically disclosed in any of Examples 1 to 50.

11. Compounds as claimed in claim 9, other than those claimed in any of claims 2 to 7, as herein specifically disclosed in any of Examples 1 to 42.

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



(II)

(wherein R_1, R_2 and Y are as defined in claim 1 and R_3 represents an alkyl group containing from 1 to 8 carbon atoms, an aralkyl group containing from 7 to 10 carbon atoms or a phenyl group) with a compound of formula III,

$$NH_2—Ar \qquad (III)$$

(wherein Ar is as defined in claim 1).

13. A process as claimed in claim 12 wherein the reaction is effected in the presence of an aromatic hydrocarbon, dimethylformamide, dimethylacetamide, dimethylsulfoxide, an ether or an excess of the compound of formula III as solvent.

14. A process as claimed in claim 13 wherein the reaction is effected in the presence of benzene, toluene, xylene, chlorobenzene, *o*-dichlorobenzene, tetrahydronaphthalene, dimethoxyethane, diethylene glycol dimethyl ether or diphenyl ether as solvent.

15. A process as claimed in claim 13 or claim 14 wherein the reaction is effected in the presence of an aromatic hydrocarbon or ether as solvent and the alcohol formed during the reaction is continuously separated from the reaction mixture.

16. A process as claimed in any of claims 12 to 15 wherein the reaction is effected at temperatures of from 60 to 200°C.

17. A process as claimed in any of claims 12 to 16, for the preparation of compounds of general formula I wherein Ar represents a thiazol-2-yl group, wherein the compound of formula III is 2-aminothiazole and the reaction is effected in the presence of a catalytic amount of a trialkyl borate, triphenylphosphine or a mixture thereof and/or under nitrogen.

18. A process as claimed in claim 17 wherein the trialkyl borate is tri-n-butyl borate.

19. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a methyl or ethyl group which comprises reacting a compound of formula I as defined in claim 1 (wherein R_1 represents a hydrogen atom) with a compound of formula IV,

$$R_1'—Hal \qquad (IV)$$

(wherein R_1' represents a methyl or ethyl group and Hal represents a halogen atom) in the presence of a base.

20. A process as claimed in claim 19 wherein the base comprises an alkali or alkaline earth metal hydroxide, carbonate or alcoholate or a tertiary amine.

21. A process as claimed in claim 20 wherein the base comprises potassium, sodium or barium hydroxide, potassium or sodium carbonate, potassium methylate, sodium methylate, sodium ethylate, potassium tert. butylate or triethylamine.

22. A process as claimed in claim 20 or claim 21 wherein the reaction is effected in the presence of water, an alcohol, dimethylformamide, dimethylacetamide, dimethylsulfoxide and/or hexamethylphosphoric acid triamide as solvent.

23. A process as claimed in claim 22 wherein the alcohol is methanol, ethanol, n-propanol or isopropanol.

24. A process as claimed in claim 20 wherein the base comprises an alkali or alkaline earth metal carbonate and the reaction is effected in the presence of an aliphatic ketone as solvent.

25. A process as claimed in claim 24 wherien the aliphatic ketone is acetone.

26. A process as claimed in claim 19 wherein the base is an alkali metal or alkaline earth metal hydride and is reacted with the compound of formula I before addition of the compound of formula IV, the reaction being effected in the

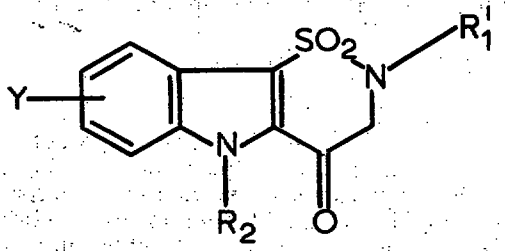
presence of an aromatic hydrocarbon or an open chain or cyclic ether as solvent.

27. A process as claimed in claim 26 wherein the base is sodium hydride.

28. A process as claimed in claim 26 or claim 27 wherein the reaction is effected in the presence of benzene or tetrahydrofuran as solvent.

29. A process as claimed in any of claims 19 to 28 wherein the reaction is effected at temperatures of from 0 to 80°C.

30. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a methyl or ethyl group and Ar represents a benzimidazol-2-yl or benzoxazol-2-yl group; an oxazol-2-yl group (optionally substituted by a methyl group) or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, trifluoromethyl or methoxy group) which comprises reacting a compound of formula V,



(V)

(wherein R_2 and Y are as defined in claim 1 and R_1' is as defined in claim 19) with a compound of formula VI,

$$Ar'—N=C=O \qquad (VI)$$

[wherein Ar' represents a benzimidazol-2-yl or benzoxazol-2-yl group; an oxazol-2-yl group (optionally substituted by a methyl group) or a phenyl group (optionally substituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, trifluoromethyl or methoxy group)] in the presence of a base or of a Grignard reagent.

31. A process as claimed in claim 30 wherein the reaction is effected in the presence of a base.

32. A process as claimed in claim 31 wherein the base comprises a tertiary amine or an alkali metal or alkaline earth metal hydride.

33. A process as claimed in claim 32 wherein the base comprises triethylamine, 1,5-diazabicyclo[4,3-0]non-5-ene or sodium hydride.

34. A process as claimed in claim 32 or claim 33 wherein the base comprises an alkali or alkaline earth metal hydride and is used in substantially equimolar quantities as compared with the compound of formula VI.

35. A process as claimed in any of claims 31 to 34 wherein the reaction is effected in the presence of an aprotic organic solvent.

36. A process as claimed in claim 35 wherein the solvent comprises dimethylformamide, dimethylacetamide, dimethylsulfoxide, hexamethylphosphoric acid triamide, tetrahydrofuran, 1,4-dioxan or an aromatic hydrocarbon.

37. A process as claimed in claim 36 wherein the solvent comprises benzene.

38. A process as claimed in any of claims 31 to 37 wherein the base and the compound of formula VI are used in molar excess with respect to the compound of formula V.

39. A process as claimed in any of claims 31 to 38 wherein the reaction is effected at from ambient temperatures to the boiling point of the reaction mixture.

40. A process as claimed in claim 30 wherein the reaction is effected in the presence of a Grignard reagent.

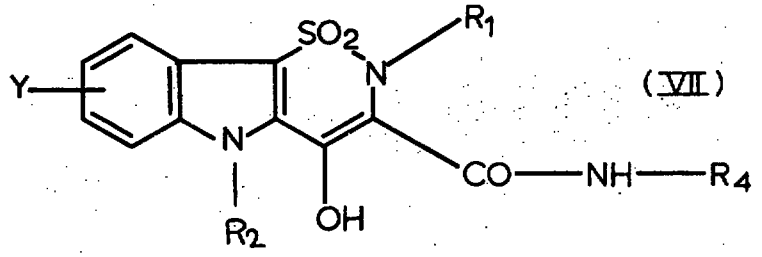
41. A process as claimed in claim 40 wherein the reaction is effected in the presence of an ether as solvent.

42. A process as claimed in claim 41 wherein the reaction is effected in the prsence of diethyl ether, dibutyl ether, tetrahydrofuran, anisole or a mixture thereof as solvent.

43. A process as claimed in any of claims 40 to 42 wherein the reaction is effected at temperatures of from −20 to +150°C.

44. A process as claimed in claim 43 wherein the reaction is effected at temperatures of from 0 to 30°C.

45. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula VII,



(VII)

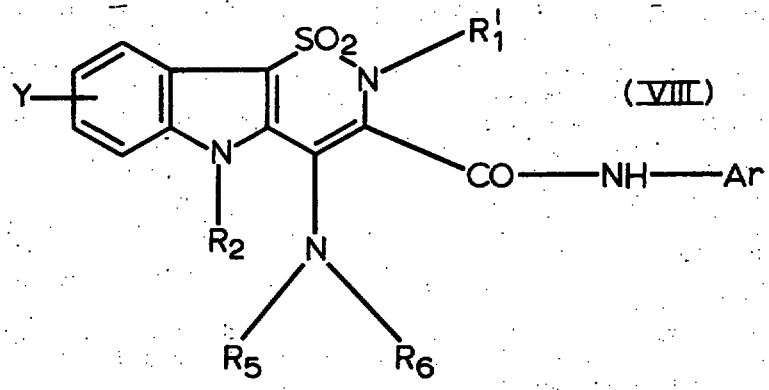
(wherein R_1, R_2 and Y are as defined in claim 1 and R_4 represents a hydrogen atom, an alkyl group containing from 1 to 8 carbon atoms, a cycloalkyl group containing from 3 to 10 carbon atoms, an aralkyl group containing from 7 to 10 carbon atoms or a phenyl group) with a compound of formula III as defined in claim 12.

46. A process as claimed in claim 45 wherein the reaction is effected in the presence of an aromatic hydrocarbon, dimethylformamide, dimethylacetamide, dimethylsulfoxide, hexamethylphosphoric acid triamide, an ether and/or an excess of the compound of formula III as solvent.

47. A process as claimed in claim 46 wherein the reaction is effected in the presence of benzene, toluene, xylene, *o*-dichlorobenzene, dimethoxyethane, diethylene glycol dimethyl ether or diphenyl ether as solvent.

48. A process as claimed in any of claims 45 to 47 wherein the reaction is effected at temperatures of from 80 to 200°C.

49. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a methyl or ethyl group which comprises hydrolysing a compound of formula VIII,



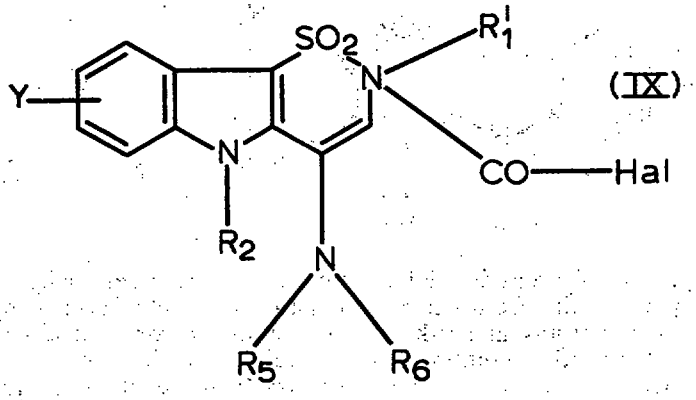
(VIII)

(wherein Y, R_2 and Ar are as defined in claim 1, R_1' is as defined in claim 19 and either R_5 and R_6, which may be the same or different, each represents an alkyl group containing from 1 to 3 carbon atoms or, together with the nitrogen atom to which they are attached, they represent a piperidino, pyrrolidino, morpholino or N-attached, they represent a piperidino, pyrrolidino, morpholino or N-methylpiperazinyl group) whereby the desired compound of formula I is obtained.

50. A process as claimed in claim 49 wherein hydrolysis is effected by heatingt the compound of formula VIII in the presence of an aqueous or aqueous-alcoholic solution of a strong or medium strong acid.

51. A process as claimed in claim 50 wherein the acid is a hydrohalic acid, phosphoric, sulfuric, methanesulfonic, *p*-toluenesulfonic or trifluoroacetic acid or mixtures thereof.

52. A process as claimed in any of claims 49 to 51 wherein the compound of formula VIII is obtained by reaction of a compound of formula IX,



(wherein Y and R_2 are as defined in claim 1, R_1' is as defined in claim 19, R_5 and R_6 are as defined in claim 49 and Hal represents a halogen atom) with a compound of formula III as defined in claim 12.

53. A process as claimed in claim 52 wherein the reaction of the compound of formula IX with the compound of formula III is effected in the presence of an ether or an aromatic hydrocarbon as solvent.

54. A process as claimed in claim 52 or claim 53 wherein the reaction of the compound of formula IX with the compound of formula III is effected at temperatures of from −40 to +80°C.

55. A process as claimed in any of claims 52 to 54 wherein the reaction of the compound of formula IX with the compound of formula III is effected in the presence of a tertiary organic base.

56. A process as claimed in claim 55 wherein the tertiary organic base is triethylamine.

57. A process as claimed in any of claims 52 to 56 wherein the compound of formula VIII is prepared *in situ*.

58. A process for the preparation of physiologically compatible salts with bases of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an appropriate base.

59. A process as claimed in claim 58 wherein the base is an alkali metal or alkaline earth metal hydroxide, an alkali metal alcoholate, a trialkylammonium hydroxide or an alkylamine.

60. A process as claimed in any of claims 12 to 59 for the preparation of compounds as claimed in claim 9.

61. A process for the preparation of compounds of general formula I as defined in claim 1 and the physiologically compatible salts thereof with bases substantially as herein described.

62. A process for the preparation of compounds of general formula I as defined in claim 1 and the physiologically compatible salts thereof with bases substantially as herein described in any of Examples 1 to 50.

63. Compounds of general formula I as defined in claim 1 and their physiologically compatible salts with bases whenever prepared by a process as claimed in any of claims 12 to 59, 61 and 62.

64. A process for the preparation of compounds of general formula I as defined in claim 9 and the physiologically compatible salts thereof with bases substantially as herein described in any of Examples 1 to 42.

65. Compounds of general formula I as defined in claim 9 and their physiologically compatible salts with bases whenever prepared by a process as claimed in claim 60 or claim 64.

66. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically compatible salt thereof with a base in association with a pharmaceutical carrier or excipient.

67. Compositions as claimed in claim 66 in a form suitable for oral, rectal or parenteral administration.

68. Compositions as claimed in claim 66 or claim 67 in the form of tablets, coated tablets, gelatin capsules, suspensions, suppositories and solutions.

69. Compositions as claimed in any of claims 66 to 68 in the form of dosage units.

70. Compositions as claimed in claim 69 wherein each dosage unit contains from 10 to 250 mg of active ingredient.

71. Compositions as claimed in claim 70 wherein each dosage unit contains from 25 to 100 mg of active ingredient.

72. Compositions as claimed in any of claims 66 to 71 wherein the active ingredient comprises a compound as claimed in any of claims 2 to 7.

73. Compositions as claimed in claim 66 wherein the active ingredient comprises a compound as claimed in claim 9.

74. Pharmaceutical compositions as claimed in claim 66 substantially as herein described.

75. Pharmaceutical compositions substantially as herein described in any of Examples I to VI.

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