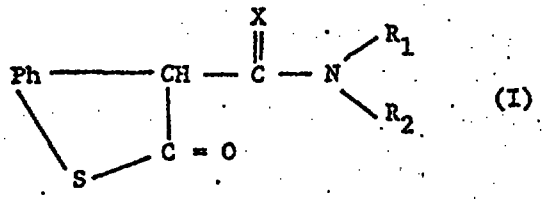
SPECIFICATION

Novel oxothia compounds, processes for their preparation, pharmaceutical preparations containing these compounds and such compounds for therapeutic use

The invention relates to oxothia compounds, especially the 2-oxo-2,3-dihydro-benzo[b]thiophen compound of the formula



(I)

in which Ph is an unsubstitued 1,2-phenylene radical, X is oxygen, R_1 is 2-thienyl and R_2 is hydrogen, and salts thereof with bases and also to processes for their preparation and pharmaceutical preparations which contain a compound of the formula I or salts thereof and such compounds for therapeutic use.

The above 2-oxo-2,3-dihydro-benzo[b]thiophen compounds can also exist in the tautomeric form, i.e. in the form of 2-hydroxy-benzo[b]thiophen compounds.

In this specification the term "lower" used to qualify organic radicals and compounds denotes that these contain not more than 7 and preferably not more than 4 carbon atoms.

Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl or tert.-butyl.

Lower alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or isobutoxy.

Halogen is in particular halogen with an atomic number of not more than 35, i.e. fluorine, chlorine or bromine.

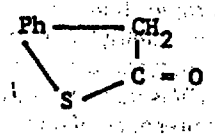
Salts of the compound of the formula I are especially pharmaceutically usable salts with bases, in particular metal salts or ammonium salts. Metal salts are in particular metal salts derived from metals of groups Ia, Ib, IIa and IIb of the periodic table of the elements, such as alkali metal salts or alkaline earth metal salts, for example sodium salts, potassium salts, magnesium salts, calcium salts, zinc salts or copper salts. Ammonium salts are in particular salts with secondary or tertiary organic bases, for example with morpholine, thiomorpholine, piperidine, pyrrolidine, dimethyl- or diethyl-amine or triethylamine, but, less importantly, also salts with ammonia. The formation of salts with the compound of the formula I probably takes place from the tautomeric 2-hydroxy-benzo[b]thiophen form.

The novel compounds have valuable pharmacological properties. Peripheral analgesic actions are in the forefront of the spectrum of action and these can be demonstrated both in mice in the phenyl-p-benzoquinone writhing test and in rats in the acetic acid writhing test, analogously to the method described by Krupp et al., Schweiz. med. Wsch., volume 105, page 646 (1975), in doses of about 1 to about 100 mg/kg administered perorally. In addition, they have anti-inflammatory actions which can be demonstrated, for example, in the kaolin oedema test on rats, analogously to the method described by Menassé and Krupp, Toxicol, Appl. Pharmacol. volume 29, page 389 (1974) in doses of about 30 mg/kg to about 100 mg/kg administered perorally. In vitro, in doses of 0.1-50 µg/ml, these compounds also inhibit the prostaglandin synthetase system to a markedly great extent (method: White and Glassman, Prostaglandins, vol. 7, No. 2, page 123 (1974)). Furthermore they have uricosuric actions, which can be demonstrated, for example, in the phenol red excretion test, analogously to the method described by Swingle et al., Arch. int. Pharmacodyn., volume 189, page 129 (1971), in doses of about 100 mg/kg administered perorally.

The compounds are therefore used as peripheral analgesics, for example for the treatment of conditions of pain of very diverse origin, or as antiphlogistic agents, for example for the treatment of arthritic inflammations, or to influence traumatic inflammatory and oncotic conditions, and also as uricosuric agents, for example for the treatment of gout.

The novel compounds also have antithrombotic actions, which can be demonstrated in rabbits in the experimental pulmonary embolism analogously to the method described by Silver et al., Science, volume 183, page 1085 (1974), in doses of about 3 mg/kg to about 30 mg/kg administered perorally. They can therefore also be used as thrombolytic agents.

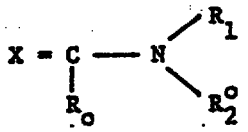
The compounds of the present invention can be prepared in a manner known per se. Thus, they are obtained, for example, by introducing a group of the formula $-C(=X)-N(R_1)(R_2)$ (Ia) into the compound of the formula



(II)

The 2-oxo-2,3-dihydro-benzo[b]thiophen starting material of the formula II can also exist in the tautomeric form, i.e. in the form of the 2-hydroxy-benzo[b]thiophen compound.

The group of the formula Ia can be introduced direct or step-wise. Thus, this group can be introduced direct by reaction with a compound of the formula III



(III)

in which R_o is an etherified or an esterified hydroxyl group or a substituted or unsubstituted amino group and R_2^o has the meaning defined for R_2, or in which R_o and R_2^o together form a bond.

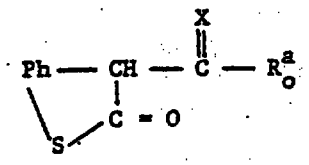
An etherified hydroxyl group R_o is preferably hydroxy etherified by a substitured or unsubstituted hydrocarbon radical, such as lower alkyl, for example methyl or ethyl, or halogeno-lower alkyl, for example 2,2,2-trichloroethyl, and in particular by substituted or unsubstituted phenyl, such as phenyl containing lower alkyl, lower alkoxy, halogen, and/or nitro, and is, for example, lower alkoxy, such as methoxy or ethoxy, halogeno-lower alkoxy, for example, 2,2,2-trichloroethoxy, or phenoxy, whilst an esterified hydroxyl group is preferably esterified by a strong mineral acid and is, in particular, halogen, especially chlorine. A substituted amino group contains, as substituents, one or preferably two substituted or unsubstituted hydrocarbon radicals, such as lower alkyl and/or phenyl, which can be substituted, for example as indicated above, and is, for example, lower alkylamino, such as methylamino or ethylamino, di-lower alkylamino, such as dimethylamino or diethylamino, or phenylamino and preferably diphenylamino, in which the phenyl radical can be substituted, for example by lower alkyl, such as methyl, lower alkoxy, for example methoxy, halogen, for example fluorine, chlorine or bromine, and/or nitro. An amino group R_o can, however, also represent the radical of the formula $-N(R_1)(R_2)$.

The above reaction is customarily carried out in the presence of a basic agent, such as of a corresponding inorganic or organic agent. Suitable inorganic bases are, in particular, salt-forming agents, expecially alkali metal salt-forming agents, such as alkali metal hydrides or alkali metal amides, and also alkali metal-organic compounds, such as corresponding lower alkanolates, and also corresponding lower alkyl compounds or phenyl compounds, for example sodium methylate, sodium ethylate, potassium tert.-butylate, n-butyl-lithium or phenyl-lithium. Suitable organic bases are in particular amines, such as tertiary amines, preferably tri-lower alkylamines, for example triethylamine, heterocyclic tertiary bases especially of the pyridine type, for example pyridine, or quaternary bases, such as tetra-lower alkyl-ammonium hydroxides or tri-lower alkyl-phenyl-lower alkyl-ammonium hydroxides. In the presence of the base, the starting material of the formula II reacts in the anionic form, i.e. in the form of a salt, with the starting material of the formula III.

The latter are carbamic acid esters, carbamic acid halides, ureas and isocyanates which correspond to the formula III.

The reaction is carried out in the presence or absence of a solvent or diluent and, if necessary, with cooling or heating, for example in a temperature range of about −10°C to about +120°C, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

The step-wise introduction of a group of the formula Ia into a starting material of the formula II can be carried out by reacting a compound of the formula II with a compound of the formula $R_o^b-C(=X)-R_o^a$ (IV) in which R_o^a and R_o^b independently of one another are an etherified or esterified hydroxyl group, and treating a compound of the formula



(IIa)

which is obtainable as an intermediate, with an amine of the formula R_1-HN-R_2 (V).

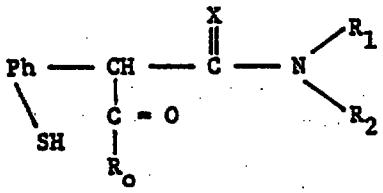
Etherified or esterified hydroxyl groups R_o^a and R_o^b have, for example, the meanings defined above for the corresponding radical R_o and are, for example, lower alkoxy, such as methoxy or ethoxy, and also substitued or unsubstituted phenoxy, or halogen, for example chlorine. Suitable compounds of the formula IV are, for example, di-lower alkyl carbonates, for example, diethyl carbonate or diphenyl carbonate, phosgene or lower alkyl halogenoformates, for example isobutyl chloroformate. The reaction of the starting material of the formula II with a compound of the formula IV is usually carried out in the presence of a base, such as one of those mentioned above, for example in the presence of an alkali metal hydride or of a tri-lower alkylamine. Usually, an intermediate of the formula IIa is not isolated but is reacted direct with the amine of the formula V.

The above process steps are carried out in the absence or presence of a solvent or diluent and, if necessary, with cooling or heating, for example in a temperature range of about −10°C to about +120°C, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

The starting material of the formula II can be obtained, for example, by reacting an enamine derived from a cyclohexanone, which is unsubstituted, with a cyanoacetate, acylating the amino group of the resulting 2-amino-4,5,6,7-tetrahydrobenzothiophen-3-carboxylate, dehydrogenating the reaction product with sulfur and treating the resulting 2-acylamino-benzothiophen-3-carboxylate with sodium hydroxide solution, or by converting a corresponding benzothiophen with butyl-lithium into the 2-lithium compound and oxidising the latter with hydrogen peroxide. Another process for the preparation of the compound of the formula II comprises converting a corresponding benzothiophen-2-carboxylate with hydrazine to the acid hydrazide, reacting the latter with nitrous acid to give the azide, rearranging this to the isocyanate, converting the isocyanate by alcoholysis to the urethane, hydrolysing the latter to the carbamic acid, decarboxylating this acid and hydrolysing the resulting 2-iminobenzothiophen.

Compounds of the formula II can be prepared, for example, by reacting compounds of the formulae $R_o^b-C(=X)-R_o^a$ (IV) and HNR_1R_2 (V).

The novel compounds can also be obtained when a compound of the formula



(VI)

in which R_o is an etherified or esterified hydroxyl group or a substituted or unsubstituted amino group, or a salt thereof, is cyclised.

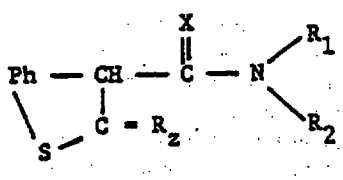
A salt of the starting material of the formula VI is, for example, an alkali metal salt.

A group R_o can be, for example, as defined above and is, for example, lower alkoxy, such as methoxy or ethoxy, halogeno-lower alkoxy, for example, 2,2,2-trichloroethoxy, substituted or unsubstituted phenoxy, or halogen, for example chlorine, or also lower alkylamino, for example methylamino, di-lower alkylamino, for example dimethylamino or diethylamino, phenylamino or diphenylamino, or also the group of the formula $-N(R_1)(R_2)$.

The above cyclisation reaction can be carried out in a manner known per se, if necessary in the presence of a condensing agent, usually a basic condensing agent, such as a salt-forming agent, for example an alkali metal salt-forming agent, inter alia including in the presence of an alkali metal lower alkanolate, for example sodium methylate, sodium ethylate, or potassium tert.-butylate. The reaction is carried out in the absence or presence of a solvent or diluent, if necessary with cooling or warming, for example in the temperature range of about 0°C to about 150°C, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

The starting materials of the formula VI can be prepared in a manner known per se, for example introducing a group of the formula $-C(=O)-R_o$ into the methylene moiety of the benzyl group of a compound of the formula $R_y-S-Ph-CH_2-R_x$ (VII), in which R_x is the radical of the formula $-C(=X)-N(R_1)(R_2)$ (Ia) and R_y is hydrogen or preferably a mercapto protective group, such as hydrogenolytically detachable α-phenyl-lower alkyl, for example benzyl, by reacting a compound of the formula VII with a suitable derivative of carbonic acid, such as a corresponding ester, for example a di-lower alkyl carbonate, such as diethyl carbonate, or diphenyl carbonate, a dihalide, for example phosgene, a halogenated ester, for example a lower alkyl halogenoformate, urea, and also isocyanate, usually in the presence of a basic agent, such as of an alkali metal hydride, alkali metal amide or alkali metal lower alkanolate, or of an organic base, for example triethylamine. A mercapto protective group can then be detached in the customary manner, for example by treating with catalytically activated hydrogen, and the mercapto group can thus be set free.

The novel compounds of the present invention can also be obtained by, in a compound of the formula



(VIII)

in which R_z is a substituted or unsubstituted imino group convertible to the oxo group by hydrolysis, hydrolysing R_z to oxo.

In a substituted imino group R_z, a substituent is, for example, a substituted or unsubstituted hydrocarbon radical, such as lower alkyl, for example methyl or ethyl, or phenyl, or an acyl group derived from a carboxylic acid or a half-ester of carbonic acid, for example lower alkanoyl, such as acetyl, or benzoyl, or

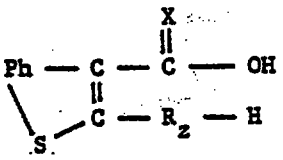
lower alkoxycarbonyl, such as methoxycarbonyl or ethoxycarbonyl.

The starting material of the formula VIII, which can also exist in the tautomeric form of a corresponding 2-(H–R_z)-benzo[b]thiophen compound, in which the group -R_z–H is an amino group which can be monosubstituted, is converted to the desired compound of the formula I by hydrolysis, preferably by treatment with water in the presence of a basic or acid agent, such as an inorganic base, for example an alkali metal hydroxide, or a mineral acid, for example hydrochloric acid or sulfuric acid.

The reaction is carried out in the presence or absence of a solvent or diluent, and if necessary with cooling or heating, for example in a temperature range of about –10°C to about +120°C, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

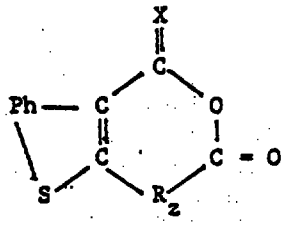
The starting material of the formula VIII can be prepared in a manner known per se, by, for example, reacting a compound of the formula

(IX)



in which R_z is preferably an unsubstituted imino group and the group -R_z–H is therefore in particular a primary amino group, with, for example, phosgene or a lower alkyl chloroformate, and treating a compound of the formula

(X)



which is thus obtainable, if desired after introducing a substituent into a hydrogen-containing imino group R_z, for example by treatment with a lower alkyl halide in the presence of a reagent which forms an alkali metal compound, with an amine of the formula R_1–HN–R_2 (V) and, if desired, in a starting material of the formula VIII in which R_z is an unsubstituted imino group, or in a tautomer thereof in which -R_z–H is an unsubstituted amino group, substituting this imino or amino group, for example by lower alkylation or acylation, the latter being effected, for example, by treatment with a suitable symmetrical, mixed or inner anhydride of a carboxylic acid.

The invention also relates to those embodiments of the process in which a compound obtainable as an intermediate at any process stage is used as the starting material and the missing process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative thereof, if desired in the form of a salt.

The starting materials used in the process of the present invention are preferably those which result in the compounds described above as being particularly valuable.

The present invention also relates to pharmaceutical preparations which contain compounds of the formula I and to such compounds for therapeutic use of the compounds, preferably in the form of pharmaceutical preparations. The pharmaceutical preparations according to the invention are those which are intended for enteral, such as oral, rectal or parenteral administration or for topical or local application to warm-blooded animals and which contain the pharmacological active ingredient on its own or together with a pharmaceutically usable carrier. The dosage of the active ingredient depends on the species of warm-blooded animal, the age and the individual condition and also on the mode of administration.

The novel pharmaceutical preparations contain from about 10% to about 90% and preferably from about 20% to about 90% of the active ingredient. Pharmaceutical preparations according to the invention are, for example, those in the form of elixirs, aerosols or sprays or in the form of dosage units, such as sugar-coated tablets, tablets, capsules, suppositories or ampoules.

The pharmaceutical preparations of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilising methods.

Preparations for oral administration can be obtained, for example, by combining the active ingredient with solid carriers, granulating a resulting mixture if desired and processing the mixture or granules, after adding suitable adjuncts if desired or necessary, to tablets or sugar-coated tablet cores. Suitable carriers are in particular fillers, such as sugar, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, using, for example, maize starch, corn starch, rice starch or potato starch,

gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above starches, and also carboxymethyl-starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Adjuncts are in particular glidants and lubricants, for example silicic acid, talc, stearic acid or salts, thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which can be resistant to gastric juices, using, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, shellac solutions in suitable organic solvents or solvent mixtures or, for the preparation of coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments can be added to the tablets or sugar-coated tablet coatings for example to identify or indicate different doses of active ingredient.

Further pharmaceutical preparations for oral administration are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerin or sorbitol. The dry-filled capsules can contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilizers can also be added.

Pharmaceutical preparations suitable for rectal administration are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Examples of suitable suppository bases are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Gelatin rectal capsules, which consist of a combination of the active ingredient with a base material, are also suitable; suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Preparations suitable for parenteral administration are in particular aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, for which suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, are used, or aqueous injection suspension which contain substances which increase the viscosity for example sodium carboxymethylcellulose, sorbitol and/or dextran, and can also contain stabilisers.

Pharmaceutical preparations for topical and local use are, for example, lotions and creams, which contain a liquid or semi-solid oil-in-water or water-in-oil emulsion, and ointments (which preferably contain a preservative), for the treatment of the skin, eyedrops, which contain the active compound in aqueous or oily solution, and eye ointments, which are preferably prepared in sterile form, for the treatment of the eyes, powders, aerosols and sprays (similar to those described above for the treatment of the respiratory passages) and coarse powders which are administered by rapid inhalation through the nostrils, and nose drops, which contain the active compound in aqueous or oily solution, for the treatment of the nose, or lozenges, which contain the active compound in a base which is generally formed from sugar and gum arabic or tragacanth and to which flavourings can be added, and also pastilles, which contain the active ingredient in an inert base, for example of gelatin and glycerin or sugar and gum arabic, for the local treatment of the mouth.

The invention also includes the novel compounds for use as anti-inflammatory agents, analgesics, uricosuric agents, anti-allergic agents and/or thrombolytic agents, preferably in the form of pharmaceutical preparations. The dails dose, which in particular is dependent on the condition of the organism to be treated and/or on the indication, is from about 300 mg to about 1 g for a warm-blooded animal weighing about 70 kg.

The following examples illustrate the invention described above; however, they are not intended to restrict the scope of the invention in any way. Temperatures are in degrees centrigrade.

Example 1:

A solution of 7.5 g of 2,3-dihydro-2-oxo-benzo[b]-thiophen in 50 ml hexamethylphosphoric acid triamide is added dropwise, with cooling, to a suspension of 2.4 g of a 50% sodium hydride/mineral oil dispersion in 100 ml of hexamethylphosphoric acid triamide, the temperature being kept below 15° during the addition. After stirring for half an hour at room temperature, 52 g of phenyl N-(2-thienyl)-carbamate, dissolved in 50 ml of hexamethylphosphoric acid triamide, are added dropwise, with external cooling. The reaction mixture is stirred for a further 16 hours at room temperatures and is poured into a mixture of 200 ml of 2N hydrochloric acid and 1000 ml of ice water. An oil separates out and this crystallises after about 2 hours. The crystalline product, which contains solvent, is dissolved in 2N sodium hydroxide solution and the solution is washed four times with ethyl acetate. The organic phase is washed with water, the aqueous phases are combined and acidified to a pH of 1 and the crude product is filtered off with suction and recrystallised from tetrahydrofuran/ether. N-(2-Thienyl)-2-oxo-2,3-dihydro-3-benzo[b]thiophen-carboxamide with a melting point of 142-144° (decomposition) is obtained.

Example 2

0.8 g of N-(2-thienyl)-2-acetamino-benzo[b]thiophen-3-carboxamide is suspended in 5 ml of ethanol, 2.5 ml of water and 2.5 ml of concentrated hydrochloric acid and the suspension is refluxed for 7 1/2 hours. The

reaction mixture is left to stand overnight at room temperature and the methanol is stripped off under reduced pressure. The evaporation residue is taken up in water, filtered off with suction and washed with water. The residue is taken up in dilute sodium hydroxide solution and insoluble material is filtered off, the aqueous phase is acidified and the N-(2-thienyl)-2-oxo-2,3-dihydro-3-benzo[b]thiophen-carboxamide with a melting point of 142-144°C (decomposition), which has precipitated, is filtered off.

The starting material can be prepared as follows:

3 g of magnesium curlings and 30 ml of anhydrous tetrahydrofuran are initially introduced into a sulfonation flask and 13.5 g of ethyl bromide are added in order to prepare ethyl-magnesium bromide. After the magnesium has dissolved, 6.1 g of 2-aminothiophen, dissolved in 60 ml of absolute tetrahydrofuran, are added dropwise and the mixture is stirred for one hour at room temperature and then refluxed for a further 15 minutes. 8 g of ethyl-2-acetamido-benzo[b]thiophen-3-carboxylate, dissolved in 100 ml of absolute tetrahydrofuran, are then added dropwise at room temperature. The mixture is then refluxed for 15 minutes and stirred for a further 15 minutes at room temperature, the reaction solution is evaporated in vacuo, dilute hydrochloric acid is added to the evaporation residue and the mixture is extracted twice with chloroform. The chloroform extracts are combined, dried over sodium sulfate and evaporated to dryness in vacuo. Crude N-(2-thienyl)-2-acetaminobenzo[b]thiophen-3-carboxamide is obtained and this can be used without further purification.

Example 3:

11.4 g of o-mercapto-phenylmalonic acid N-(2-thienyl)-amide in 50 ml of dimethylformamide and 1 ml of concentrated hydrochloric acid are heated at 100° for 2 hours. The mixture is allowed to cool, 100 ml of water are added and the precipitate is filtered off with suction and taken up in 100 ml of diethyl ether. N-(2-thienyl)-2-oxo-2,3-dihydro-3-benzo[b]thiophen-carboxamide with a melting point of 142-144° (decomposition) is obtained from the organic phases after washing, first with 1N sodium hydroxide solution and then with water, drying over sodium sulfate and evaporating, subjecting the residue to chromatography and crystallising the product from ether.

The starting material can, for example, be prepared as follows:

A vigorous stream of air is passed through a solution of 9.4 g of o-mertcaptophenylacetic acid in 56 ml of N sodium hydroxide solution for 8 hours, with stirring. The reaction mixture is evaporated to dryness in a rotary evaporator. Twice 50 ml of toluene are added to the residue, the mixture being evaporated to dryness after each addition. The residue is then dried at 50° under a high vacuum for 90 minutes and suspended in 180 ml of dimethylformamide, and 7 g of dimethyl sulfate are added to the suspension in the course of 3 minutes, with stirring. The reaction mixture is heated at 110° for 1 hour, with stirring, and is then cooled and poured onto ice. The suspension formed is extracted with ethyl acetate and the organic phases are combined and washed with water, dried over sodium sulfate and evaporated. The residue (18 g) is dissolved in 200 ml of dimethylformamide and this solution is added dropwise to a suspension of 4.8 g of 50% sodium hydride in 200 ml of dimethylformamide. The mixture is stirred, with gentle warming, until the evolution of hydrogen has ceased. A solution of 15 g of 2-thienyl isocyanate in 100 ml of dimethylformamide is then added dropwise slowly at 0°. The solution is stirred for a further 24 hours at room temperature and ice and dilute hydrochloric acid are then added. The product which then separates out is extracted with ethyl acetate and the extract is washed with water, dried over sodium sulfate and evaporated.
o,o'-Bis-[α-methoxycarbonyl-N-(2-thienyl)-carbamylmethyl]-diphenyl disulfide is obtained and this can be employed without purification.

20.0 g of crude o,o'-bis-[α-methoxycarbonyl-N-(2-thienyl)-carbamyl-methyl]-diphenyl disulfide are suspended in 300 ml of ethanol and 7 g of sodium borohydride are added in portions, with stirring. The mixture is stirred at room temperature for 4 hours and evaporated, water is added to the residue and the mixture is acidified with hydrochloric acid until it just gives an acid reaction to congo red and extracted with ethyl acetate. On evaporation, crude o-mercapto-phenylmalonic acid N-(2-thienyl)-amide is obtained and this can be cyclised without further purification.

Example 4:

Tablets containing 0.1 g of N-(2-thienyl)-2-oxo-2,3-dihydro-3-benz[b]-thiophen-carboxamide are prepared as follows:

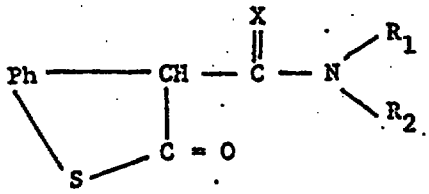
Composition (for 1000 tablets):

N-(2-Thienyl)-2-oxo-2,3-dihydro-3-benzo[b]thiophen-carboxamide	100.00 g
Lactose	50.00 g
Corn starch	73.00 g
Colloidal silica	13.00 g
Magnesium stearate	2.00 g
Talc	12.00 g
Water	q.s.

The N-(2-thienyl)-2-oxo2,3-dihydro-3-benzo[b]thiophen-carboxamide is mixed with a portion of the corn starch and with the lactose and the colloidal silica and the mixture is forced through a sieve. A further portion of the corn starch is mixed to a paste with five times the amount of water on a water bath and the above powder mixture is kneaded with this paste until a slightly plastic mass has formed. The plastic mass is forced through a sieve of about 3 mm mesh width and dried and the dry granules are again forced through a sieve. The remainder of the corn starch, the talc and the magnesium stearate are then mixed in and the resulting mixture is compressed to tablets weighting 0.25 g.

CLAIMS

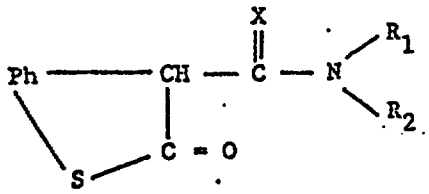
1. The 2-oxo-2,3-dihydro-benzo[b]thiophen compound of the formula



(I)

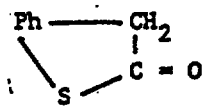
in which Ph is an unsubstituted 1,2-phenylene radical, X is oxygen, R_1 is 2-thienyl and R_2 is hydrogen, and salts thereof with bases.

2. A compound of the formula I according to claim 1 in the tautomeric 2-hydroxy-benzo[b]thiophen form.
3. A pharmaceutical preparation containing one of the compounds as claimed in claims 1 and 2.
4. A process for the preparation of the 2-oxo,2,3-dihydrobenzo[b]thiophen compound of the formula



(I)

in which Ph is an unsubstituted 1,2-phenylene radial, X is oxygen, R_1 is 2-thienyl and R_2 is hydrogen, and salts thereof with bases, which comprises introducing a group of the formula $-C(=X)-N(R_1)(R_2)$ (Ia) into the compound of the formula



(II)

Example 4:

Tablets containing 0.1 g of N-(2-thienyl)-2-oxo-2,3-dihydro-3-benz[b]-thiophen-carboxamide are prepared as follows:

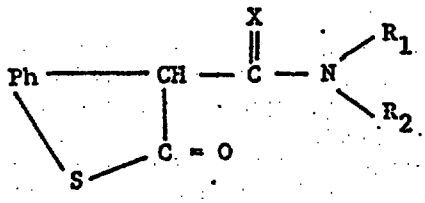
Composition (for 1000 tablets):

N-(2-Thienyl)-2-oxo-2,3-dihydro-3-benzo[b]thiophen-carboxamide	100.00 g
Lactose	50.00 g
Corn starch	73.00 g
Colloidal silica	13.00 g
Magnesium stearate	2.00 g
Talc	12.00 g
Water	q.s.

The N-(2-thienyl)-2-oxo2,3-dihydro-3-benzo[b]thiophen-carboxamide is mixed with a portion of the corn starch and with the lactose and the colloidal silica and the mixture is forced through a sieve. A further portion of the corn starch is mixed to a paste with five times the amount of water on a water bath and the above powder mixture is kneaded with this paste until a slightly plastic mass has formed. The plastic mass is forced through a sieve of about 3 mm mesh width and dried and the dry granules are again forced through a sieve. The remainder of the corn starch, the talc and the magnesium stearate are then mixed in and the resulting mixture is compressed to tablets weighting 0.25 g.

CLAIMS

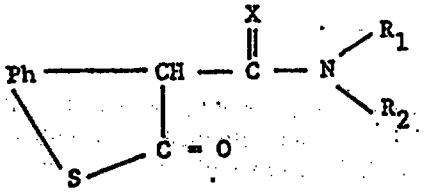
1. The 2-oxo-2,3-dihydro-benzo[b]thiophen compound of the formula



(I)

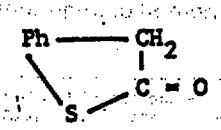
in which Ph is an unsubstituted 1,2-phenylene radical, X is oxygen, R_1 is 2-thienyl and R_2 is hydrogen, and salts thereof with bases.

2. A compound of the formula I according to claim 1 in the tautomeric 2-hydroxy-benzo[b]thiophen form.
3. A pharmaceutical preparation containing one of the compounds as claimed in claims 1 and 2.
4. A process for the preparation of the 2-oxo,2,3-dihydrobenzo[b]thiophen compound of the formula



(I)

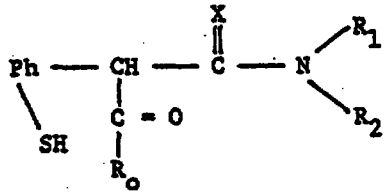
in which Ph is an unsubstituted 1,2-phenylene radial, X is oxygen, R_1 is 2-thienyl and R_2 is hydrogen, and salts thereof with bases, which comprises introducing a group of the formula $-C(=X)-N(R_1)(R_2)$ (Ia) into the compound of the formula



(II)

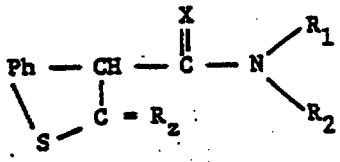
or cyclising a compound of the formula

(IV)



in which R_o is an etherified or an esterified hydroxyl group or a substituted or unsubstituted amino group, or a salt thereof, or, in a compound of the formula

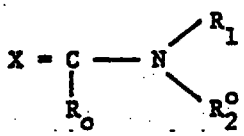
(VIII)



in which R_z is a substituted or unsubstituted imino group which is convertible to the oxo group by hydrolysis, hydrolysing R_z to oxo, and, if desired, converting the resulting free compound into a salt or converting a resulting salt into the free compound or into another salt.

5. A process according to claim 4, wherein the radical of the formula Ia is introduced into a starting material of the formula II by reacting a compound of the formula II with a compound of the formula

(III)

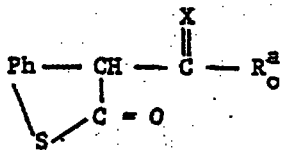


in which R_o is an etherified or esterified hydroxyl group or a substituted or unsubstituted amino group and R_2^o has the meaning defined for R_2 or in which R_o and R_2^o together form a bond.

6. A process according to claim 5, wherein the compound of the formula III which is employed is carbamate, a carbamic acid halide or an isocyanate.

7. A process accoding to claim 4, wherein the radical of the formula Ia is introduced into a starting material of the formula II by reacting a compound of the formula II with a compound of the formula $R_o^b-C(:X)-R_o^a$ (IV), in which R_o^a and R_o^b independently of one another are an etherified or esterified hydroxyl group, and treating a compound of the formula

(IIa)



which is obtainable as an intermediate, with an amine of the formula R_1-HN-R_2 (V).

8. A process as claimed in claim 4 carried out substantially as described in Example 1 herein.

9. A process as claimed in claim 4 carried out substantially as described in any one of Examples 2 and 3 herein.

10. A compound as claimed in claim 1 obtainable by the process of any one of claims 4 to 9.

11. A compound as claimed in claim 1 obtainable by the process of any one of Examples 1 to 3.

12. A compound as claimed in any one of claims 1, 2, 10 and 11, or a pharmaceutical preparation as claimed in claim 3 for use as an anti-inflammatory agent, an analgesic, a uricosuric agent, an anti-allergic agent, and/or an anti-thrombolytic agent in a method of treatment of the human or animal body by therapy.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1982.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

ERRATUM

SPECIFICATION NO 2024220B

Front page Heading (54) Title of invention
after **compounds and** ***delete*** **their use as a medicinal active compound**
insert **such compounds for therapeutic use**

THE PATENT OFFICE
27 January 1983