The invention relates to new 2-(2-thienyl)-imidazo(4,5-c)pyridine derivatives of the general formula of the formula sheet,
wherein R_1 denotes lower alkyl, R_2 denotes hydrogen or methyl and n denotes 0 or 1, and the pharmaceutically usable acid addition salts of compounds of the general formula I, a process for their preparation, pharmaceutical products containing these compounds and their use in medicaments.

The expression "lower alkyl" used in this description means straight-chain or branched hydrocarbon radicals with 1 to 4 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl.

In a preferred class of compounds of the general formula I, R_1 denotes methyl or ethyl, and R_2 particularly preferably denotes methyl.

Particularly preferred individual compounds of the general formula I are 2-(3-methoxy-5-methylthio-2-thienyl)-1H-imidazo(4,5-c)pyridine, 2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo(4,5-c)pyridine and the hydrochlorides of these compounds.

The 2-(2-thienyl)-imidazo(4,5-c)pyridine derivatives of the general formula I and salts thereof are preferably prepared, according to the invention, by methods which are known per se, by a process in which
a) a thiophenecarboxylic acid derivative of the general formula II of the formula sheet, 2
wherein R_1 has the meaning given in the case of formula I, or a salt thereof is converted into a thiophenecarboxylic acid chloride of the general formula III of the formula sheet, 2
wherein R_1 has the meaning given in the case of formula I, by reaction with an inorganic acid chloride, this product is reacted with a diaminopyridine of the general formula IV of the formula sheet, 2
wherein R_2 is as defined in formula I, to give an isomer mixture consisting of the amides of the general formula V of the formula sheet, 2

wherein R_1 and R_2 are as defined in formula I, one of the symbols A and B denotes the =N atom and the other in each case denotes a =CH ring member of the pyridine ring, the free bases in the resulting isomer mixture are converted into the hydrochlorides and these are cyclized with dehydrating agents to form the imidazole ring, after which

b) if appropriate, a resulting compound of the general formula I wherein n denotes 0 is converted into a compound of the general formula I in which n denotes the number 1 by treatment with organic peracids or hydrogen peroxide, and

c) if desired, a compound of the general formula I obtained in process step (a) or (b) or a salt thereof which cannot be used pharmaceutically is converted into a pharmaceutically usable addition salt with inorganic or organic acids.

The preparation of the thiophenecarboxylic acid chlorides of the general formula III in process step (a) is advantageously carried out by reaction of a thiophenecarboxylic acid of the general formula II with an inorganic acid chloride, for example thionyl chloride, phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride, at low temperatures, the reaction with thionyl chloride at temperatures of about $0^{\circ}C$ being particularly preferred.

A thiophenecarboxylic acid chloride of the general formula III obtained in the above reaction is subsequently reacted, according to the invention, with a 3,4-diaminopyridine of the general formula IV under the reaction conditions customary for amide formation, an isomer mixture containing the amides represented by formula V being formed. The reaction of compounds of the formula III with those of the formula IV is advantageously carried out in a suitable organic solvent, preferably in pyridine, with the addition of a strong base, and the use of triethylamine has proved to be particularly advantageous for this purpose. For simplicity, the amides of the formula V can be prepared at

room temperature, but temperatures which are just above or below room temperature are suitable, in the same manner per se, for the reaction.

The compounds of the general formula V obtained in this reaction in the isomer mixture in the form of the free bases are converted into the hydrochloride before the cyclization, this conversion advantageously being effected by introducing HCl gas into a solution of the free bases in an inert organic solvent and subsequently precipitating the hydrochlorides, for example by addition of dry diethyl ether, and the hydrochlorides are then cyclized to compounds of the general formula I wherein n denotes 0 in accordance with process step (a) by treatment with a dehydrating agent, the imidazole ring being formed.

The cyrlization can also be carried out by direct treatment of the mixture of the hydrochlorides of the compounds of the general formula V or advantageously by treatment of suspensions thereof in a suitable organic solvent or diluent, suspensions of the hydrochlorides in pyridine having proved to be particularly suitable. Possible dehydrating agents are the reagents usually employed for such cyclization reactions, for example phosphorus oxychloride, phosphorus pentachloride or thionyl chloride and the like.

The dehydrating reagent can be used for this purpose in equivalent amounts or, advantageously, in an excess, for example in amounts of 1.1 to 5 mol per mol of the mixture of the formula V. Slow addition of a 1.5- to 3-fold molar excess of phosphorus oxychloride to a suspension of the hydrochlorides of amides of the general formula V at room temperature or temperatures just above or below room temperature have proved to be a particularly advantageous cyclization method for the preparation of the compounds according to the invention.

According to process step (b), the sulfonyl compounds in which n in the general formula I denotes the number 1 can be obtained by partial oxidation of the methylmercapto compounds of the general formula I, where n denotes 0, obtained by process step (a), with

suitable oxidizing agents. Oxidizing agents which are used are preferably approximately equivalent amounts of an organic peracid, such as peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and the like, in a solvent which is inert in the reaction, for example methylene chloride or chloroform, advantageously at temperatures between -5°C and -50°C, preferably at about 0°C, or approximately equivalent amounts of 30% strength hydrogen peroxide in glacial acetic acid, advantageously at room temperature.

The compounds of the general formula I obtained by process step (a) or (b) have strongly basic properties. They can easily be converted into crystalline, pharmaceutically usable acid addition salts in the customary manner with inorganic or organic acids in accordance with process step (c), and the salts, such as, for example, the hydrochlorides, can readily be purified by recrystallization. For this, the crude base is advantageously dissolved in a suitable solvent, for example a lower aliphatic alcohol, an equivalent amount of the desired acid is added, the salts formed are precipitated or the solvent is evaporated off in vacuo and the residue is recrystallized from methanol or ethanol, if appropriate with the addition of ether or acetone.

Suitable examples of such pharmaceutically usable salts of compounds of the formula I are, in addition to the salt of hydrochloric acid, for example the salts of sulfuric acid, nitric acid, sulfonic acids, benzoic acid, maleic acid, tartaric acid and citric acid and of similar acids which have already been used for the preparation of pharmaceutically usable salts of known compounds.

The thiophenecarboxylic acid derivatives of the general formula II used as starting materials for the process for the preparation of the compounds according to the invention are known from the literature (European Patent A-0,148,742) or can be prepared in a manner which is known per se, starting from known

compounds. The diaminopyridines of the general formula IV are likewise known and, inter alia, are commercially available (for example from Fluka AG, Buchs, Switzerland).

The new compounds of the general formula I and similarly their pharmaceutically usable acid addition salts exhibit extremely useful pharmacological properties both in vitro and in vivo in animal experiments. In particular, they have a strongly positive inotropic action on the heart and, as a result of their cardiotonic properties, they can therefore be used in human medicine for the treatment and prophylaxis of diseases of the heart and vessels, in particular for the treatment of myocardial insufficiency and pathological consecutive symptoms thereof.

To ascertain these pharmacological properties, compounds according to the invention were subjected to the following generally recognized pharmacological investigations:

1) Positively inotropic action on the isolated guinea-pig auricle

The action of compounds of the general formula I on the frequency and contraction force of freshly prepared isolated guinea-pig auricles was tested. For this, the test substances were investigated in concentrations in the range from 10^{-7} to 3.10^{-4} mol/l, the auricles of untreated animals being used in a first series of experiments and those of animals treated with reserpine being used in a second series of experiments.

Result:

In this standard text, compounds according to the invention had the effect of a significant dose-dependent increase in the contraction force of isolated, electrically stimulated, left auricles from guinea pigs. For example, the compound of the general formula I, 2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo(4,5-c)pyridine hydrochloride, effects a 50% increase in the contraction force at a concentration of 1.2×10^{-4} mol/l. The effect on the contraction force

is thus qualitatively comparable to that of the known cardiac glycoside quabaine, that is to say 3-((6-deoxy-alpha-L-mannopyranosyl)oxy)1,5,11 alpha, 14,19-penta-hydroxy-card-20(22)-enolide.

In comparison with quabaine, the compounds according to the invention, such as 2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo(4,5-c)pyridine hydrochloride, have the advantage that even in the upper concentration range investigated, no therapeutically undesirable increase in rate occurs on the spontaneously beating right auricle from guinea pigs.

Pretreatment with reserpine only slightly impairs the action of the substances investigated, so that a direct action mechanism can be assumed for the compounds according to the invention. Compounds of the general formula I accordingly exhibit a clear, direct positively inotropic action, coupled with only a very weak positively chronotropic action, on the isolated auricle of guinea pigs.

B) Investigations on anesthetized dogs

Compounds according to the invention were injected in doses of 3 to 3,000 ug/kg cumulatively into the v. jugularis of beagle dogs anesthetized with alpha chloralose (1,2-O-(2,2,2-trichloroethylidene)-alpha-D-glucofuranose). After the administration, the action on the left ventricular pressure (LV dp/dt), the femoralis pressure and flow, the cardiac output (CO) and the heart rate was investigated.

Result:

In these investigations, the compounds according to the invention effect on the one hand a significant dose-dependent increase in the left ventricular pressure and the cardiac output, and on the other hand a decrease in the left ventricular end diastolic pressure and the peripheral diastolic blood pressure.

Thus, for example, 2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo(4,5-c)pyridine hydrochloride already leads to a marked increase in the left ventricular pressure (LV dp/dt = +113%), without an undesir-

able influence on the heart rate, at a dose of 300 ug/kg. At this dose, the substance exhibits a significant, strongly positively inotropic action on anesthetized dogs. A clear increase in heart rate occurs only at doses of 1 to 3 mg/kg intravenously, which are far outside the therapeutic use range.

Cardiac glycosides or sympathomimetic amines have to date been administered as substances with a positively inotropic action. Cardiac glycosides caused side effects, such as dangerous cardiac disrhythmia, in many cases and must be used with care, because of their high toxicity. Sympathomimetic amines have only limited possible uses, inter alia because of their positively chronotropic side effect, arhythmogenic properties and oral ineffectiveness. Because of their pronounced and at the same time very specific positively inotropic action, the substances according to the invention thus respresent an interesting class of new active compounds which could replace, with great advantage to the patient, the products previously used for the treatment of myocardial insufficiency.

On the basis of their favorable properties, the compounds of the general formula I and salts thereof can be used as medicines, for example in the form of pharmaceutical products which contain the compounds according to the invention mixed with a pharmaceutical, organic or inorganic excipient suitable for enteral or parenteral administration, for example water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, vegetable or animal fats, polyalkylene glycols, vaseline and the like. The pharmaceutical products can be in solid form, for example in the form of tablets, coated tablets, suppositories or capsules, or in liquid form, for example in the form of solutions, suspensions or emulsions. If appropriate, they are sterilized and/or contain auxiliaries, such as preservatives, stabilizers or emulsifying agents and salts for modifying the osmotic pressure. In particular, they can also be administered in combination with other

therapeutically useful substances.

The following examples illustrate the invention in more detail:

Example 1:

2-(3-methoxy-5-methylthio-2-thienyl)-1H-imidazo(4,5-c)-pyridine

4.0 g (19.6 mmol) of 3-methoxy-5-methylthio-2-thiophenecarboxylic acid are stirred into 40 ml of $SOCl_2$ at 0°C, the mixture is stirred for 20 minutes and the excess solvent is evaporated off at room temperature in vacuo.

The crude acid chloride (4.3 g, melting point = 98-101°C, diisopropyl ether) is dissolved in 25 ml of dry benzene and the solution is added dropwise to a mixture of 2.1 g (19.6 mmol) of 3,4-diaminopyridine, 14 ml of absolute pyridine and 10 ml of triethylamine at 20°C in the course of 10 minutes. The mixtures is stirred at room temperature for a further 90 minutes. The reaction mixture is largely evaporated, the residue is diluted with 50 ml of water and the mixture is acidified to pH 4 with 2 N HCl, brought to pH 7 with $NaHCO_3$ and extracted three times with a total of 200 ml of ethyl acetate. The combined organic phases are dried over sodium sulfate and filtered and the filtrate is concentrated to 50 ml. HCl gas is passed at a temperature of less than 30°C into the solution which remains, until this is saturated, and 250 ml of dry diethyl ether are then added. The oil which has separated out is decanted and is washed twice more with 100 ml of dry ether each time and freed from residual ether in vacuo.

The mixture of the amides is suspended in 50 ml of absolute pyridine, and 5.76 g (37.6 mmol) of $POCl_3$ are added dropwise at 20°C in the course of 5 minutes, with stirring. The mixture is stirred at room temperature for a further 90 minutes. It is then largely evaporated and the residue is partitioned between 50 ml of saturated $NaHCO_3$ solution and 50 ml of ethyl acetate. The aqueous phase is extracted twice more with 40 ml of

ethyl acetate each time and the combined organic phases are dried over sodium sulfate and evaporated. The residue (2.8 g) is taken up in 150 ml of methanol, excess methanolic hydrochloric acid is added, the mixture is filtered hot, after addition of active charcoal, the solution is concentrated to about 50 ml and cooled and the yellow hydrochloride which has precipitated out is filtered out with suction, washed with a little cold methanol and dried in vacuo (1.6 g).

To prepare the free base, 1.6 g (5.10 mmol) of the hydrochloride are suspended in 12 ml of methanol, excess aqueous ammonia is added and the product is precipitated by addition of 40 ml of water. It is filtered off with suction, washed with water and dried at 60°C/20 mbar.

Yield: 1.27 g

Melting point = 165-167°C (2-butanone/Et_2O = 3:1).

Example 2:

2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo (4,5-c)pyridine

0.50 g (1.80 mmol) of 2-(3-methoxy-5-methylthio-2-thienyl)-1H-imidazo(4,5-c)pyridine is dissolved in 30 ml of chloroform, the solution is cooled to -10°C and a solution of 0.40 g (1.98 mmol) of 85% strength 3-chloroperbenzoic acid in 10 ml of chloroform is added dropwise at this temperature in the course of 10 minutes, with stirring. The mixture is stirred at -10°C for a further 10 minutes and extracted twice with 8 ml of saturated $NaHCO_3$ solution each time and the organic phase is dried over sodium sulfate and evaporated.

Yield: 0.46 g (87%)

Melting point = 235°C (methanol)

Example 3:

2-(3-methoxy-5-methylthio-2-thienyl)-1H-imidazo(4,5-c)-pyridine hydrochloride

1.0 g (3.6 mmol) of 2-(3-methoxy-5-methylthio-2-thienyl)-1H-imidazo-(4,5-c)pyridine are suspended in 25 ml of methanol, and 7 ml of 1 N methanolic HCl are added. The mixture is evaporated to dryness in vacuo

and the residue is recrystallized from methanol.

Yield: 1.04 g (92%)

Melting point = 234-236°C (decomposition; methanol)

Example 4:

2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo-(4,5-c)pyridine hydrochloride

0.4 g (1.36 mmol) of 2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo(4,5-c)pyridine is suspended in 13 ml of methanol, and 3 ml of 1 N methanolic HCl are added. The mixture is evaporated to dryness and the residue is recrystallized from methanol/acetone.

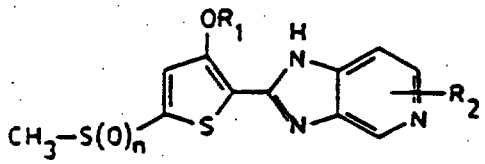
Yield: 0.37 g (83%)

Melting point = 204-207°C (methanol/acetone)

Patent Claims

for the Contracting States BE,CH,DE,FR,GB,IT,LI,LU,NL,SE

1. 2-(2-Thienyl)-imidazo(4,5-c)pyridine derivatives of the general formula I



I

wherein R_1 denotes C_1-C_4alkyl, R_2 denotes hydrogen or methyl and n denotes 0 or 1, and the pharmaceutically usable acid addition salts of compounds of the general formula I.

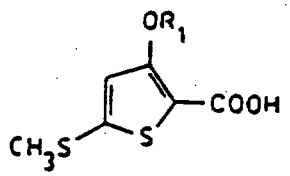
2. Compounds of the general formula I defined in claim 1, wherein R_1 denotes methyl or ethyl.

3. The compounds according to claim 1, 2-(3-methoxy-5-methylthio-2-thienyl)-1H-imidazo(4,5-c)pyridine and the hydrochloride thereof.

4. The compounds according to claim 1, 2-(3-methoxy-5-methylsulfinyl-2-thienyl)-1H-imidazo(4,5-c)pyridine and the hydrochloride thereof.

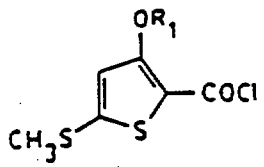
5. Process for the preparation of compounds of the general formula I defined in claim 1, characterized in that

a) a thiophenecarboxylic acid derivative of the general formula II



II

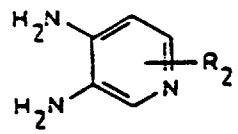
wherein R_1 has the meaning given in the case of formula I, or a salt thereof is converted into a thiophenecarboxylic acid chloride of the general formula III



III

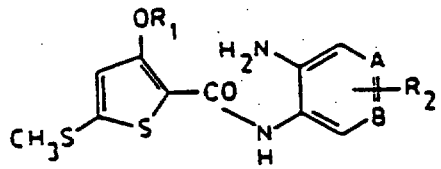
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wherein R_1 has the meaning given in the case of formula I, by reaction with an inorganic acid chloride, this product is reacted with a diaminopyridine of the general formula IV



IV

wherein R_2 is as defined in formula I, to give an isomer mixture consisting of the amides of the general formula V



V

wherein R_1 and R_2 are as defined in formula I, one of the symbols A and B denotes the =N atom and the other in each case denotes a =CH ring member of the pyridine ring, the free bases in the resulting isomer mixture are converted into the hydrochlorides and these are cyclized with dehydrating agents to form the imidazole ring, after which

b) if appropriate, a resulting compound of the general formula I wherein n denotes 0 is converted into a compound of the general formula I in which n denotes the number 1 by treatment with organic peracids or hydrogen peroxide, and

c) if desired, a compound of the general formula I obtained in process step (a) or (b) or a salt thereof which cannot be used pharmaceutically is converted into a pharmaceutically usable addition salt with inorganic or organic acids.

6. Pharmaceutical products containing compounds of the general formula I according to claim 1 or acid addition salts thereof in combination with the auxiliaries and excipients customary in galenics.

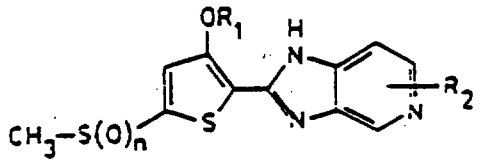
7. Compounds of the general formula I according to claim 1 or acid addition salts thereof as active com-

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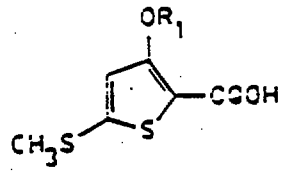
pounds for pharmaceutical products with a positively inotropic action.

8. Compounds according to claim 1 or acid addition salts thereof for use as active compounds for medicaments for the treatment or prophylaxis of diseases of the heart and circulation, in particular myocardial insufficiency.

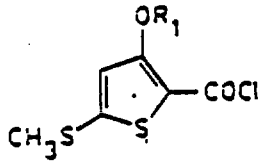
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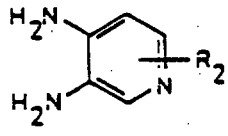
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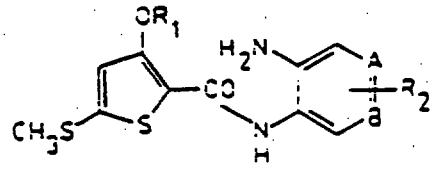
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III



IV



V

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