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(54) PHARMACEUTICAL PREPARATIONS FOR THE TREATMENT OF CORONARY HEART DISEASES

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

The present invention relates to new pharmaceutical preparations which contain, as pharmacological active compounds, a beta-receptor-blocking compound and a compound which regulates the thrombocyte function and, optionally, an alpha-receptor-blocking compound.

The new pharmaceutical preparations are suitable, above all, for the prophylactic and therapeutic treatment of coronary heart diseases, especially of an arteriosclerotic nature, which can also be accompanied by thrombosis. They can be used in the various stages of arteriosclerotic coronary heart disease, that is to say angina pectoris, coronary insufficiency and cardiac infarction.

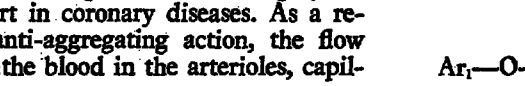
The beta-receptor-blocking component of the new pharmaceutical preparations effects a lowering of the heart rate, a reduction in the cardiac contractility and screening of the heart from subjection to external adrenergic stimuli, which results in a reduction of the myocardial oxygen consumption and, in the case of critical nutrition, has the effect of conserving tissue. Compounds which have thrombocyte function-regulating properties effect a reduction in the metabolic rate of the thrombocytes, that is to say in the rate at which the thrombocytes are produced and die off, and prolong their survival period, especially when the latter is shortened due to disease. In addition, they reduce the increase in adhesiveness and aggregation of the blood platelets produced by pathological influences. These properties reduce or prevent thrombotic processes which play an important part in coronary diseases. As a result of the anti-aggregating action, the flow properties of the blood in the arterioles, capillaries and venules are also decisively improved, which, in turn, leads to an improvement in the oxygen supply.

The alpha-receptor-blocking compound which is optionally added to the combination of a beta-receptor-blocking compound and a compound which regulates the thrombocyte function, has the effect, by means of peripheral vasodilatation, of facilitating the stroke output and thus relieving the left hand ventricle, with a corresponding additional reduction in the oxygen consumption.

The combined use of the two types of active compound, to which a compound with an alpha-receptor-blocking action can also optionally be added, considerably increases the probability of the therapeutic success, since the actions of the pharmacologically active components supplement one another in a surprising manner.

These pharmaceutical preparations provide a new principle for the prophylactic and therapeutic treatment of coronary heart diseases. This principle is that the oxygen consumption of the myocardium is reduced by beta-blocking, and thrombotic processes in the coronary arteries are reduced or prevented and the flow properties of the blood are improved because the formation of thrombocyte aggregates is prevented. The combination of these effects leads to an unexpected improvement in the results of treatment. The preparation to be manufactured according to the invention display a good long-term toleration, cause no troublesome side effects and, in particular due to the reduction in the frequency of cardiac infarction, represent a distinct and considerable advance in the therapy of coronary heart diseases.

The compounds with beta-receptor-blocking properties which are employed in the pharmaceutical preparations of the invention are those of the formula



wherein Ar_1 represents a monocyclic or polycyclic, carbocyclic or heterocyclic radical which contains at least one ring of aromatic character, and which is bonded to the oxygen atom via a ring carbon atom, preferably of the ring of aromatic character, R_1 denotes an optionally substituted aliphatic, cycloaliphatic or araliphatic hydrocarbon radical and R_2 represents hydrogen or the acyl radical of an organic carboxylic acid, as well as salts thereof which can be used pharmaceutically, above all corresponding acid addition salts thereof.

Carbocyclic radicals Ar_1 of aromatic character are, above all, phenyl, as well as optionally partially saturated bicyclic aromatic hydrocarbon radicals, such as naphthyl, for example 1- or 2 - naphthyl, 1,2,3,4 - tetrahydro - *benz* - naphthyl, for example 1,2,3,4 - tetrahydro - 5 - naphthyl, *benz* - indenyl, for example 4- or 5 - indenyl, and also optionally partially saturated polycyclic aromatic hydrocarbon radicals, such as *benz* - fluorenyl, for example 4 - fluorenyl, partially saturated radicals of the above type being bonded to the oxygen atom via a ring carbon atom of the aromatic part.

Heterocyclic radicals Ar_1 contain, as ring hetero-atoms, above all one or more ring nitrogen atoms as well as, preferably in addition to a ring nitrogen atom, a ring oxygen atom or ring sulphur atom. Such radicals are, in particular, monocyclic, five-membered or six-membered, mono-, di- or tri - azacyclic radicals, above all monocyclic, monoazacyclic, six-membered radicals of aromatic character, such as pyridyl, for example 2-, 3- or 4 - pyridyl, monocyclic, diazacyclic, six-membered radicals of aromatic character, such as pyridazinyl, for example 3 - pyridazinyl, pyrimidinyl, for example 2- or 4 - pyrimidinyl, or pyrazinyl, for example 2 - pyrazinyl, monocyclic, thiadiazacyclic, five-membered radicals of aromatic character, such as thiadiazolyl, for example 1,2,5 - thiazol - 3 - yl, optionally partially saturated bicyclic, monoazacyclic radicals of aromatic character with a five-membered or six-membered heterocyclic ring, such as indolyl, for example 4 indolyl, or optionally partially saturated quinolinyl, for example 1,2,3,4 - tetrahydro - 5 -quinolinyl, or bicyclic monothiacyclic radicals of partially aromatic character, such as 2H - thiochromenyl, for example 2H - thiochromen - 8 - yl.

The above radicals Ar_1 can be unsubstituted or substituted and Ar_1 contains, above all, one, or also several, in particular two, substituents. The latter are, above all, optionally substituted aliphatic or cycloaliphatic hydrocarbon radicals, optionally etherified or esterified hydroxy or mercapto groups, acyl radicals, optionally functionally modified carboxyl groups, nitro or optionally substituted amino groups. Saturated parts of the group Ar_1 can also contain, in addition to the abovementioned substituents, substituents which have two bonds, above all oxo.

As substituents of the radical Ar_1, aliphatic hydrocarbon radicals are, in particular, lower alkyl or lower alkenyl, as well as lower alkinyl. Substituent of such radicals, especially of lower alkyl, as well as lower alkenyl, are optionally etherified or esterified hydroxyl, for example lower alkoxy, lower alkylthio or halogen, optionally functionally modified carboxyl, especially optionally N - substituted carbamoyl such as N - lower alkylated carbamoyl, or optionally substituted amino, especially acylamino, wherein acyl represents the radical of an organic carboxylic acid or of a carbonic acid half-derivative, as well as of an organic sulphonic acid, such as lower alkanoylamino, lower alkoxycarbonylamino or optionally N - substituted ureido, such as N' - lower alkylated ureido, for example ureido, N' - lower alkyl - ureido or N',N' - di - lower alkyl - ureido, and also lower alkylsulphonylamino. Substituted lower alkyl radicals are, above all, hydroxy - lower alkyl, lower alkoxy - lower alkyl, lower alkylthio - lower alkyl, halogeno - lower alkyl, optionally N - lower alkylated carbamoyl - lower alkyl, lower alkanoylamino - lower alkyl or lower alkoxycarbonylamino - lower alkyl, and also lower alkanoylamino - lower alkenyl or lower alkoxycarbonylamino - lower alkenyl.

Cycloaliphatic hydrocarbon radicals are presented, in particular, by monocyclic and polycyclic cycloalkyl.

As substituents of a radical Ar_1, etherified hydroxyl or mercapto groups are, above all, hydroxyl or mercapto which are etherified by optionally substituted aliphatic hydrocarbon radicals, such as lower alkoxy, lower alkenyloxy or lower alkinyloxy, and also lower alkylthio or lower alkenylthio. Substituents of such etherifying aliphatic hydrocarbon radicals, especially of etherifying lower alkyl, are, above all, optionally etherified or esterified hydroxyl or mercapto, such as lower alkoxy, lower alkylthio or halogen, or optionally substituted amino, such as acylamino, for example lower alkanoylamino or lower alkoxycarbonylamino. Hydroxyl or mercapto etherified by correspondingly substituted aliphatic hydrocarbon radicals is, in particular, lower alkoxy - lower alkoxy, lower alkylthio - lower alkoxy or lower alkoxy - lower alkylthio and also lower alkanoylamino - lower alkoxy or lower alkoxycarbonylamino - lower alkoxy.

As substituents of groups Ar_1, esterified hydroxyl or mercapto groups are, above all, halogen as well as lower alkanoyloxy.

As substituents of the radical Ar_1, acyl groups represent, above all, lower alkanoyl.

As substituents of Ar_1, optionally functionally modified carboxyl groups are, in particular, esterified or amidated carboxyl and also cyano. Esterified carboxyl is, above all, lower alkoxycarbonyl, whilst amidated car-

boxyl represents optionally substituted carbamoyl, such as carbamoyl, N - lower alkyl - carbamoyl or N,N - di - lower alkyl - carbamoyl.

As substituents of groups Ar_1, optionally substituted amino groups are, in particular, acylamino, wherein acyl above all represents the corresponding radical of an organic carboxylic acid or of a half-derivative of carbonic acid, and also of an organic sulphonic acid, such as lower alkanoylamino, lower alkoxycarbonylamino or optionally N' - lower alkylated ureido, for example ureido, N' - lower alkyl - ureido or N',N' - di - lower alkyl - ureido, and also lower alkylsulphonylamino as well as N - lower alkylated amino, such as N - lower alkylamino or N,N - di - lower alkylamino, and furthermore, N,N - lower alkyleneamino, N,N - aza - lower alkyleneamino, N,N - oxa - lower alkyleneamino or N,N - thia - lower alkyleneamino.

Aliphatic hydrocarbon radicals R_1 are, above all, lower alkyl, especially lower alkyl branched at the linking carbon, and also lower alkenyl or lower alkinyl, whilst cycloaliphatic hydrocarbon radicals represent, in particular, cycloalkyl, including polycyclic cycloalkyl, and araliphatic hydrocarbon radicals represent, above all, phenyl - lower alkyl. Substituents of such hydrocarbon radicals are, for example for lower alkyl, etherified hydroxyl, especially phenoxy or pyridyloxy which are optionally substituted, for example by functionally modified carboxyl, such as optionally N - lower alkylated carbamoyl, for example carbamoyl, N - lower alkyl - carbamoyl, or N,N - di - lower alkyl - carbamoyl, or optionally functionally modified carboxyl, such as carboxyl and esterified carboxyl, for example lower alkoxycarbonyl, amidated carboxyl, such as optionally N - lower alkylated carbamoyl, for example, carbamoyl, N - lower alkyl - carbamoyl or N,N - di - lower alkyl - carbamoyl, or cyano, and, for example for the aromatic part of phenyl - lower alkyl, optionally functionally modified carboxyl, above all amidated carboxyl, such as carbamoyl, N - lower alkyl - carbamoyl or N,N - di - lower alkylcarbamoyl. Lower alkyl radicals substituted in this way are phenoxy - lower alkyl or preferably optionally N - alkylated carbamoylphenoxy - lower alkyl, and also pyridyloxy - lower alkyl or preferably optionally N - lower alkylated carbamoylpyridyloxy - lower alkyl and also lower alkoxycarbonyl - lower alkyl, optionally N - lower alkylated carbamoyl - lower alkyl or cyano - lower alkyl.

An acyl radical R_2 is, above all, the corresponding radical of an organic carboxylic acid, especially lower alkanoyl or benzoyl.

Unless specific data are given, the radicals and compounds designated "lower" in the preceding and following text preferably contain up to 7 carbon atoms, monovalent radicals contain above all up to 5 carbon atoms and divalent radicals contain 3 to 6, above all 4 or 5, carbon atoms.

Unless specific data are given, the general concepts used in the preceding and the following text preferably have the following meanings:

Lower alkyl is, for example, methyl, ethyl, n - propyl, isopropyl, n - butyl, isobutyl, sec. - butyl or tert. - butyl as well as n - pentyl, isopentyl, neopentyl, n - hexyl, isohexyl or n - heptyl. Lower alkyl branched at the linking carbon atom is, above all, isopropyl or tert. - butyl.

Lower alkenyl is, above all, allyl and also vinyl, 2 - methyl - allyl, 2 - butenyl or 3,3 - dimethylallyl, whilst lower alkinyl is, for example, ethinyl or propargyl.

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

Lower alkylthio is, for example, methylthio, ethylthio, isopropylthio or n - butylthio.

Halogen is, for example, chlorine or bromine and also fluorine as well as iodine.

Optionally N - lower alkylated carbamoyl is, for example carbamoyl and also N - lower alkyl - carbamoyl, such as N - methyl - carbamoyl or N - ethyl - carbamoyl, or N,N - di - lower alkyl - carbamoyl, such as N,N - dimethyl - carbamoyl or N,N - diethyl - carbamoyl.

Lower alkanoylamino is, for example, formylamino, acetylamino, propionylamino, butyrylamino or pivaloylamino.

Lower alkoxycarbonylamino is, for example, methoxycarbonylamino, ethoxycarbonylamino or tert. - butoxycarbonylamino, whilst N' - lower alkyl - ureido and N,N' - di - lower alkyl - ureido are, for example, N' - methylureido, N' - ethylureido, N',N' - dimethylureido or N',N' - diethylureido.

Lower alkylsulphonylamino is, for example, methylsulphonylamino or ethylsulphonylamino.

Hydroxy - lower alkyl is, for example, hydroxymethyl or 1- or 2 - hydroxyethyl.

Lower alkoxy - lower alkyl is, for example, lower alkoxy - methyl or, preferably, 2 - (lower alkoxy) - ethyl, such as methoxy - methyl, ethoxymethyl, 2 - methoxy - ethyl, 2 - ethoxy - ethyl or 2 - isopropoxy - ethyl.

Lower alkylthio - lower alkyl is, for example, lower alkylthio - methyl or, in particular, 2 - (lower alkylthio) - ethyl, for example methylthiomethyl, ethylthiomethyl, 2 - methylthioethyl or 2 - ethylthioethyl.

Halogeno - lower alkyl is, in particular, trifluoromethyl.

Optionally N - lower alkylated carbamoyl - lower alkyl is, for example, carbamoylmethyl or 1- or 2 - carbamoylethyl and also N - lower alkyl - carbamoyl - lower alkyl, such as N - methylcarbamoylmethyl or 1- or 2 - N - methylcarbamoyl - ethyl, or N,N - di - lower alkyl - carbamoyl - lower alkyl, such as N,N -

dimethylcarbamoyl - methyl or 1- or 2 - N,N - dimethylcarbamoyl - ethyl.

Lower alkanoylamino - lower alkyl is, for example, lower alkanoylaminomethyl or, preferably, 2 - lower alkanoylaminoethyl, such as acetylaminomethyl, propionylaminomethyl, 2 - acetylaminoethyl, 2 - propionylaminoethyl or 2 - pivaloylaminoethyl, whilst lower alkoxycarbonylamino - lower alkyl represents, for example, lower alkoxycarbonylamino - methyl or, preferably, 2 - lower alkoxycarbonylamino - ethyl, such as methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, 2 - methoxycarbonylaminoethyl, 2 - ethoxycarbonylaminoethyl or 2 - tert. - butoxycarbonylaminoethyl.

Lower alkanoylamino - lower alkenyl is, in particular, 2 - lower alkanoylamino - vinyl, for example 2 - acetylamino - vinyl, 2 - propionylamino - vinyl or 2 - pivaloylamino - vinyl, whilst lower alkoxycarbonylamino - lower alkenyl preferably represents 2 - lower alkoxycarbonylamino - vinyl, such as 2 - methoxycarbonylamino - vinyl, 2 - ethoxycarbonylamino - vinyl or 2 - tert. - butoxycarbonylamino - vinyl.

Cycloalkyl, including polycyclic cycloalkyl, preferably contains 3—10 ring carbon atoms and denotes cyclopropyl or, in particular, cyclopentyl or cyclohexyl, as well as adamantyl, such as 1 - adamantyl.

Lower alkenyloxy is, in particular, allyloxy as well as 2 - methylallyloxy, and also vinyloxy, 2 - butenyloxy or 3,3 - dimethylallyloxy, whilst lower alkinyloxy represents, for example, propargyloxy.

Lower alkenylthio is, for example, allylthio and also 2 - methyl - allylthio or 2 - butenylthio.

In a lower alkoxy - lower alkoxy radical the two oxygen atoms are preferably separated by at least 2, for example by 2—3, carbon atoms; such radicals are thus, for example, methoxymethoxy or ethoxymethoxy but above all 2 - (lower alkoxy) - ethoxy, for example 2 - methoxyethoxy or 2 - ethoxyethoxy, as well as 3 - (lower alkoxy) - propoxy, for example 3 - methoxy - propoxy or 3 - ethoxy - propoxy.

In a lower alkylthio - lower alkoxy radical the sulphur atom and the oxygen atom are preferably separated from one another by at least 2, for example by 2—3, carbon atoms; such radicals are thus, above all, 2 - (lower alkylthio) - ethoxy, for example 2 - methylthio - ethoxy or 2 - ethylthio - ethoxy.

In a lower alkoxy - lower alkylthio radical the oxygen atom and the sulphur atom are likewise preferably separated from one another by at least 2, for example by 2—3, carbon atoms; such radicals are, above all, 2 - (lower alkoxy) - ethylthio, for example 2 - methoxy - ethylthio or 2 - ethoxy - ethylthio.

In lower alkanoylamino - lower alkoxy radicals and lower alkoxycarbonylamino - lower alkoxy radicals the nitrogen atom and the linking oxygen atom are preferably separated from one another by at least 2, for example 2—3, carbon atoms; these radicals are, above all, 2 - lower alkanoylamino - ethoxy, for example 2 - acetylamino - ethoxy, 2 - propionylamino - ethoxy or 2 - pivaloylamino - ethoxy, or 2 - lower alkoxycarbonylamino - ethoxy, for example 2 - methoxycarbonylamino - ethoxy or 2 - ethoxycarbonylamino - ethoxy.

Lower alkanoyloxy is, for example, acetyloxy, propionyloxy or pivaloyloxy.

Lower alkanoyl is, in particular, acetyl, propionyl or pivaloyl.

Lower alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl or tert. - butoxycarbonyl.

N - lower alkylamino and N,N - di - lower alkylamino are, for example, methylamino, ethylamino, dimethylamino or diethylamino.

N,N - Lower alkylene amino preferably contains 5—7 ring members and is, in particular, pyrrolidino or piperidino, whilst N,N - aza - lower alkyleneamino, - N,N - oxa - lower alkyleneamino and N,N - thia - lower alkyleneamino preferably contain 6 ring members, the second ring hetero - atom being separated from the linking nitrogen atom by 2 carbon atoms and, in the N,N - aza - lower alkyleneamino radical, being optionally substituted, for example by lower alkyl; such radicals are, for example, 4 - methyl - 1 - piperazinyl, 4 - morpholino or 4 - thiomorpholino.

Phenyl - lower alkyl is, for example, benzyl or 1- or 2 - phenylethyl.

Pyridyloxy is, for example, 2 - pyridyloxy, 3 - pyridyloxy or 4 - pyridyloxy.

In a phenoxy - lower alkyl radical and pyridyloxy - lower alkyl radical R_1, which preferably contain optionally N - lower alkylated carbamoyl as substituents, the oxygen atom and the linking carbon atom bonded to the nitrogen atom are preferably separated from one another by at least 2, for example by 2—3, carbon atoms. Such substituents are, in particular, 2 - (optionally N - lower alkylated carbamoyl - phenoxy) - lower alkyl, for example 2 - (2 - carbamoylphenoxy) - ethyl, 2 - (4 - carbamoylphenoxy) - ethyl, 2 - (2 - N - methylcarbamoyl - phenyl) - ethyl or 2 - (4 - N,N - dimethylcarbamoyl - phenoxy) - ethyl, and also 2 - (optionally N - lower alkylated carbamoyl - pyridyloxy) - lower alkyl, for example 2 - (4 - carbamoyl - 2 - pyridyloxy) - ethyl, 2 - (2 - carbamoyl - 4 - pyridyloxy) - ethyl or 2 - (3 - carbamoyl - 2 - pyridyloxy) - ethyl.

Lower alkoxycarbonyl - lower alkyl is, for example, lower alkoxycarbonylmethyl or 1 - lower alkoxycarbonyl - 2 - propyl, for example methoxycarbonylmethyl, ethoxycarbonylmethyl, 1 - methoxycarbonyl - 2 - propyl or 1 - ethoxycarbonyl - 2 - propyl.

Optionally N - lower alkylated carbamoyl - lower alkyl is, above all, carbamoylmethyl and also N - lower alkylcarbamoyl - methyl, or N,N - di - lower alkylcarbamoyl - methyl, for example N - methylcarbamoylmethyl, N - ethylcarbamoylmethyl, N,N - dimethylcarbamoylmethyl or N,N - diethylcarbamoylmethyl, as well as 1 - carbamoyl - 2 - propyl and also 1 - N - lower alkyl - carbamoyl - 2 - propyl or 1 - N,N - di - lower alkyl - carbamoyl - 2 - propyl, for example 1 - N - methylcarbamoyl - 2 - propyl, 1 - N - ethylcarbamoyl - 2 - propyl, 1 - N,N - dimethylcarbamoyl - 2 - propyl or 1 - N,N - diethylcarbamoyl - 2 - propyl.

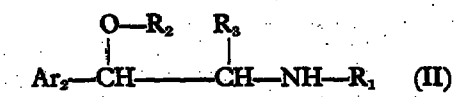
Cyano - lower alkyl is, for example, cyanomethyl or 1 - cyano - 2 - propyl.

In the compounds of the formula I, the group Ar_1 preferably denotes naphthyl, for example 1 - naphthyl, fluorenyl, for example 4 - fluorenyl, indolyl, for example 4 - indolyl, 2H - thiochromenyl, for example 2H - 8 - thiochromenyl, lower alkyl - phenyl, such as methyl - phenyl, for example 2- or 3 - methyl - phenyl, halogeno - lower alkyl - phenyl, such as chloromethyl - phenyl, for example 2 - chloro - 5 - methyl - phenyl, lower alkenyl - phenyl, such as allylphenyl, for example 2 - allylphenyl, lower alkinyl - phenyl, such as ethinyl - phenyl, for example 2 - ethinyl - phenyl, cycloalkyl - phenyl, for example 2 - cyclopropyl - phenyl or 2 - cyclopentyl - phenyl, hydroxy - lower alkyl - phenyl, for example 2 - hydroxymethyl - phenyl, lower alkoxy - lower alkyl - phenyl, such as lower alkoxymethyl - phenyl or (2 - lower alkoxy - ethyl) - phenyl, for example 2 - methoxymethyl - phenyl or 4 - (2 - methoxyethyl) - phenyl, carbamoyl - lower alkyl - phenyl, for example carbamoylmethyl - phenyl, lower alkoxy - carbonylamino - lower alkyl - phenyl, such as (2 - lower alkoxy - carbonylamino - ethyl) - phenyl, for example 4 - (2 - methoxycarbonylamino - ethyl) - phenyl, halogeno - lower alkoxycarbonylamino - lower alkyl - pyridyl, for example 3 - chloro - 4 - (2 - methoxycarbonylaminoethyl) - 2 - pyridyl, lower alkoxycarbonylamino - lower alkenylphenyl, especially (2 - lower alkoxycarbonylamino - vinyl) - phenyl, for example 4 - (2 - methoxycarbonylamino - vinyl) - phenyl, lower alkoxy - phenyl, such as methoxyphenyl, for example 2 - methoxyphenyl, lower alkenyloxy - phenyl, such as allyloxy - phenyl, for example 2 - allyloxy - phenyl, or methallyloxy - phenyl, for example 2 - (2 - methallyloxy) - phenyl, lower alkinyloxy - phenyl, such as propargyloxy - phenyl, for example 2 - propargyloxy - phenyl, lower alkylthio - lower alkoxy - phenyl wherein the sulphur atom is separated from the oxygen atom by 2—3 carbon atoms, such as (2 - lower alkylthio - ethoxy) - phenyl, for example 4 - (2 - methylthio - ethoxy) - phenyl, lower alkylthio - phenyl, such as methylthio - phenyl, for example 2 - methylthiophenyl, halogeno - phenyl, such as chlorophenyl, for example 2 - chlorophenyl, lower alkanoyl - lower alkanoylamino - phenyl, for example 2 - acetyl - 4 - n - butyrylamino - phenyl, cyano - phenyl, for example 2 - cyano - phenyl, lower alkanoylamino - phenyl, such as acetylamino - phenyl, for example 4 - acetylamino - phenyl, lower alkylsulphonylamino - phenyl, for example 4 - methylsulphonylamino - phenyl, (1 - pyrryl) - phenyl, for example 2 - (1 - pyrryl) - phenyl, morpholinothiadiazolyl, for example 4 - morpholino - 1,2,5 - thiadiazol - 3 - yl, oxo - 5,6,7,8 - tetrahydro - *benz* - naphthyl, for example 5 - oxo - 5,6,7,8 - tetrahydro - 1 - naphthyl, or oxo - 1,2,3,4 - tetrahydro - *benz* - quinolyl, for example 2 - oxo - 1,2,3,4 - tetrahydro - 5 - quinolinyl, R_2 represents, in particular, hydrogen or lower alkanoyl, for example acetyl or pivaloyl, and R_1 is, above all, lower alkyl, especially lower alkyl branched at the linking carbon, for example isopropyl or tert. - butyl, and also carbamoylphenoxy - lower alkyl, such as 2 - carbamoylphenoxy - lower alkyl, for example 2 - (4 - carbamoylphenoxy) - ethyl.

Compounds with beta - receptor - blocking properties, of the above formula I, are, above all, the following compounds in which lower alkyl R_1 is branched at the linking carbon atom: 1 - (naphthyloxy) - 3 - lower alkylamino - 2 - propanol, for example 3 - isopropylamino - 1 - (1 - naphthyloxy) - 2 - propanol, 1 - (*benz* - fluorenyloxy) - 3 - lower alkylamino - 2 - propanol and the corresponding O - esters thereof with lower alkanecarboxyl acids, for example 1 - (4 - fluorenyloxy) - 3 - isopropylamino - 2 - propanol or 3 - tert. - butylamino - 1 - (4 - fluorenyloxy) - 2 - pivaloyloxy - propane, 1 - (*benz* - indolyloxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, 3 - lower alkylamino - 1 - (2H - *benz* - thiochromenyloxy) - 2 - propanols, for example 3 - tert. - butylamino - 1 - (2H - thiochromen - 8 - yloxy) - 2 - propanol, 3 - lower alkylamino - 1 - (lower alkyl - phenoxy) - 2 - propanols wherein the phenyl radical can additionally be substituted by halogen, for example 3 - isopropylamino - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - (2 - chloro - 5 - methylphenoxy) - 3 - isopropylamino - 2 - propanol or 2 - tert. - butylamino - 1 - (2 - chloro - 5 - methylphenoxy) - 2 - propanol, 3 - (carbamoylphenoxy - lower alkylamino) - 1 - lower alkyl - phenyl) - 2 - propanols, for example 3 - [2 - (4 - carbamoylphenoxy) - ethylamino] - 1 - (2 - methylphenyl) - 2 - propanol, 1 - (lower alkenyl - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (2 - allyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (lower alkinyl - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (2 - ethinyl -

phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (cycloalkyl - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (2 - cyclopropyl - phenoxy) - 3 - isopropylamino - 2 - propanol or 3 - tert. - butylamino - 1 - (2 - cyclopentylphenoxy) - 2 - propanol, 1 - (hydroxy - lower alkyl - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (2 - hydroxymethyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (lower alkoxy - lower alkylphenoxy) - 3 -lower alkylamino - 2 - propanols, for example 3 - isopropylamino - 1 - (2 - methoxymethyl - phenoxy) - 2 - propanol, 3 - tert. - butylamino - 1 - (2 - methoxymethyl - phenoxy) - 2 - propanol or 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol, 1 - (carbamoyl - lower alkyl - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (4 - carbamoylmethyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (lower alkoxycarbonylamino - lower alkyl - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 3 - isopropylamino - 1 - [4 - (2 - methoxycarbonylamino - ethyl) - phenoxy] - 2 - propanol, 1 - (halogeno - lower alkoxycarbonylamino - lower alkyl - pyridyloxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - [3 - chloro - 4 - (2 - methoxycarbonylamino - ethyl) - 2 - pyridyloxy] - 3 - isopropylamino - 2 - propanol, 1 - (lower alkoxy - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example - 3 - isopropylamino - 1 - (2 - methoxy - phenoxy) - 2 - propanol, 1 - (lower alkenyloxyphenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (2 - allyloxy - phenoxy) - 3 - tert. - butylamino - 2 - propanol or 3 - isopropylamino - 1 - (2 - methylallyloxy - phenoxy) - 2 - propanol, 1 - (lower alkinyloxy - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 3 - isopropylamino - 1 - (2 - propargyloxy - phenoxy) - 2 - propanol, 3 - lower alkylamino - 1 - (lower alkylthio - lower alkoxy - phenoxy) - 2 - propanols, wherein the sulphur atom is separated from the oxygen atom by 2—3 carbon atoms, for example 3 - isopropylamino - 1 - [4 - (2 - methylthioethoxy) - phenoxy] - 2 - propanol, 1 - (halogeno - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 3 - tert. - butylamino - 1 - (2 - chloro - phenoxy) - 2 - propanol, 1 - (lower alkylthio - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 3 - isopropylamino - 1 - (2 - methylthio - phenoxy) - 2 - propanol, 1 - (lower alkanoyl - lower alkanoylamino - phenoxy) - 3 - lower alkylamino - 2 - propanol, for example 1 - (2 - acetyl - 4 - n - butyrylamino - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (cyano - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 3 - tert. - butylamino - 1 - (2 - cyano - phenoxy) - 2 - propanol or 1 - (2 - cyano - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (lower alkanoylamino - phenoxy) - 3 - lower alkylamino - 2 - propanols, for example 1 - (4 - acetylamino - phenoxy) - 3 - isopropylamino - 2 - propanol, 3 - lower alkylamino - 1 - (lower alkylsulphonylamino - phenoxy) - 2 - propanols, for example 3 - isopropylamino - 1 - (4 - methylsulphonylamino - phenoxy) - 2 - propanol, 1 - (morpholino - thiadiazolyloxy) - 3 - lower alkylamino - 2 - propanol, for example 3 - isopropylamino - 1 - (4 - morpholino - 1,2,5 - thiadiazol - 3 - yloxy) - 2 - propanol, 3 - lower alkylamino - 1 - (oxo - 5,6,7,8 - tetrahydro - *benz* -naphthyloxy) - 2 - propanols, for example 3 - isopropylamino - 1 - (5 - oxo - 5,6,7,8 - tetrahydro - 1 - naphthyloxy) - 2 - propanol, or 3 - lower alkylamino - 1 - (oxo - 1,2,3,4 - tetrahydro - benz - quinolinyloxy) - 2 -propanols, for example 3 - isopropylamino - 1 - (2 - oxo - 1,2,3,4 - tetrahydro - 5 - quinolinyloxy) - 2 - propanol or 3 - tert. - butylamino - 1 - (2 - oxo - 1,2,3,4 - tetrahydro - 5 - quinolinyloxy) - 2 - propanol, and acid addition salts thereof which can be used pharmaceutically.

A further group of beta - receptor - blocking compounds can be represented by the formula



(II)

wherein R_1 and R_2 have the abovementioned meanings, Ar_2 represents a monocyclic or polycyclic, carbocyclic radical which conatins at least one ring of aromatic character and R_3 denotes hydrogen or lower alkyl, and also comprises the salts thereof which can be used pharmaceutically, above all the corresponding acid addition salts thereof.

A carbocyclic radical Ar_2 of aromatic character has, for example, the meaning indicated above for the group Ar_1 and is, above all, phenyl, as well as an optionally partially saturated, bicyclic, aromatic hydrocarbon radical, such as naphthyl, for example 1- or 2 - naphthyl, 1,2,3,4 - tetrahydro - *benz* - naphthyl, or benz - indanyl, for example 4- or 5 - indanyl, and such radicals can be substituted, for example like the corresponding groups Ar_1, and contain, above all, halogen, lower alkyl, lower alkoxy, lower alkylsulphonylamino and/or nitro, for example the corresponding substituents described above.

A group R_1 in the above compounds of the formula II is, above all, lower alkyl, especially lower alkyl branched at the linking carbon atoms, above all isopropyl or tert. - butyl.

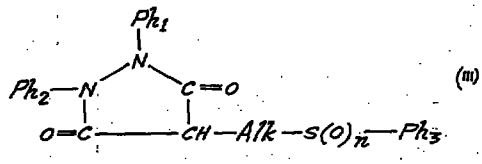
In addition to hydrogen, R_2 also represents lower alkanoyl, for example acetyl or pivaloyl.

The radical R_3 denotes hydrogen or lower alkyl, especially methyl.

In the above compounds of the formula II, Ar_2 represents, for example, naphthyl, for example 1 - naphthyl, lower alkoxy - phenyl, for example 2,5 - dimethoxy - phenyl, halogenophenyl, for example 3,4 - dichlorophenyl, nitrophenyl, for example 4 - nitrophenyl, lower alkylsulphonylamino - phenyl, for example 4 - methylsulphonylamino - phenyl, carbamoyl - hydroxy - phenyl, for example 4 - carbamoyl - 3 - hydroxyphenyl, or 1,2,3,4 - tetrahydro - *benz* - naphthyl, for example 1,2,3,4 - tetrahydro - 5 - naphthyl, R_1 denotes, above all, lower alkyl branched at the linking carbon atoms, for example isopropyl or tert. - butyl, R_2 is, in particular, hydrogen and R_3 represents, above all, hydrogen or methyl.

Compounds of the above structural formula II which have beta - receptor - blocking properties are, above all, the following compounds in which lower alkyl R_1 is branched at the linking carbon atom: 1 - (naphthyl) - 2 - lower alkylamino - ethanols, for example 2 - isopropylamino - 1 - (1 - naphthyl) - ethanol, 1 - (lower alkoxyphenyl) - 2 - lower alkylamino - ethanols, for example 2 - tert. - butylamino - 1 - (2,5 - dimethoxy - phenyl) - ethanol, 1 - (halogenophenyl) - 2 - lower alkylamino - ethanols, for example 1 - (3,4 - dichlorophenyl) - 2 - isopropylamino - ethanol, 2 - lower alkylamino - 1 - (nitrophenyl) - 2 - propanols, for example 2 - isopropylamino - 1 - (4 - nitrophenyl) - propanol, 2 - lower alkylamino - 1 - (lower alkylsulphonylamino - phenyl) - ethanols, for example 2 - isopropylamino - 1 - (4 - methylsulphonylamino - phenyl) - ethanol, 1 - (carbamoylhydroxyphenyl) - 2 - lower alkylamino - ethanols, for example 1 - (4 - carbamoyl - 3 - hydroxyphenyl) - 2 - isopropylamino - ethanol or 1 - (4 - carbamoyl - 3 - hydroxyphenyl) - 2 - tert. - butylamino - ethanol, 2 - lower alkylamino - 1 - (1,2,3,4 - tetrahydro - *benz* - naphthyl) - ethanols, for example 2 - tert. - butylamino - 1 - (1,2,3,4 - tetrahydro - 5 - naphthyl) - ethanol, and acid addition salts thereof which can be used pharmaceutically.

Compounds with thrombocyte - function - regulating properties which are employed in the pharmaceutical preparations of the invention are O - acetyl - salicylic acid, or salts thereof with bases, which can be used pharmaceutically, 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]pyrimidine (dipyramidol) or acid addition salts thereof which can be used pharmaceutically, compounds of the formula



(III)

wherein each of the radicals Ph_1 and Ph_2 independently of one another represents a phenyl radical which is optionally substituted by lower alkyl, for example methyl, hydroxyl, lower alkoxy, for example methoxy, and/or halogen, especially fluorine, chlorine or bromine, Alk denotes a lower alkylene radical which separates the sulphur atom from the ring carbon atom by at least 2 carbon atoms, *n* represents 0, 1 or 2 and Ph_3 represents a phenyl radical which is optionally substituted by lower alkyl, for example methyl, lower alkoxy, for example methoxy, and/or halogen, for example fluorine, chlorine or bromine, and salts of such compounds with bases, which can be used pharmaceutically. These compounds exhibit pronounced thrombocyte - function - regulating properties, there being no influence or only an insignificant influence on the blood coagulation time.

Lower alkylene Alk in the above compounds preferably contains up to 4 carbon atoms and is, for example, 1- or 2 - methyl - 1,2 - ethylene, 1,3 - propylene, 2 - methyl - 1,3 - propylene, 1,4 - butylene and, above all, 1,2 - ethylene.

The thrombocyte - function - regulating properties are particularly pronounced in compounds of the formula III wherein one of the radicals Ph_1 and Ph_2 denotes phenyl or hydroxy - phenyl, especially 4 - hydroxy - phenyl, and the other denotes phenyl or lower alkyl - phenyl, especially 3 - methyl - phenyl, Alk represents lower alkylene with up to 4 carbon atoms, which separates the sulphur atom from the ring nitrogen atom by 2 to 4 carbon atoms, especially 1,2 - ethylene, *n* denotes 0, 1 or 2, especially 1, and Ph_3 represents phenyl, and salts of such compounds with bases, which can be used pharmaceutically.

1,2 - Diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine and 1 - (4 - hydroxy - phenyl) - 2 - phenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, and salts of these compounds with bases, which can be used pharmaceutically, are mentioned in particular as preferred compounds with platelet - function - regulating properties.

The compounds with alpha - receptor - blocking properties, which may be optionally added to the combination, according to the invention, of a beta - receptor - blocking active compound and an active compound which regulates the thrombocyte function, are hydrogenated ergot alkaloids, for example dihydroergotamine, dihydroergocornine, dihydroergocristine or dihydroergocryptine or mixtures thereof, as well as acid addition salts thereof which can be used pharmaceutically, and also N - benzyl - N - halogeno - lower alkylamines, for example N,N - dibenzyl - N - (2 - chloroethyl) - amine or N - benzyl - N - (2 - chloroethyl) - N - (1 - methyl - 2 - phenoxy - ethyl) - amine, 2 - tert. - amino-

methyl - benzo - dioxanes, for example 2 - piperidinomethyl - benzodioxane or 1,4 - bis - (2 - benzodioxanylmethyl) - piperazine, N - substituted dibenzazepines, for example 6 - allyl - 6,7 - dihydro - 5H - dibenz[c,e] - azepine, or, in particular, methyl - 2 - imidazolines which are substituted in the 2-position, such as 2 - benzyl - imidazolines and, above all, 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, as well as pharmaceutically usable acid addition salts of such compounds.

Acid addition salts, which can be used pharmaceutically, of the abovementioned compounds are those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example acetic acid, propionic acid, glycollic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4 - amino - salicylic acid, 2 - phenoxybenzoic acid, 2 - acetoxy - benzoic acid, embonic acid, nicotinic acid or isonicotinic acid, or organic sulphonic acids, for example methanesulphonic acid, ethanesulphonic acid, 2 - hydroxy - ethanesulphonic acid, ethane - 1,2 - disulphonic acid, benzenesulphonic acid, 4 - methylbenzenesulphonic acid or naphthalene - 2 - sulphonic acid.

Salts of the abovementioned compounds with bases are, above all, metal salts or ammonium salts, such as alkali metal salts and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, as well as ammonium salts with ammonia or suitable organic amines, possible bases for salt formation being, above all, aliphatic, cycloaliphatic, cycloaliphatic - aliphatic or araliphatic primary, secondary or tertiary monoamines, diamines or polyamines, as well as heterocyclic bases, such as lower alkylamines, for example triethylamine, hydroxy - lower alkylamines, for example 2 - hydroxyethylamine, bis (2 - hydroxyethyl) - amine or tris - (2 - hydroxyethyl) - amine, basic aliphatic esters of carboxylic acids, for example 4 - aminobenzoic acid 2 - diethylamino ethyl ester, lower alkyleneamines, for example 1 - ethyl - piperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N' - dibenzyl - ethylenediamine, and also bases of the pyridine type, for example pyridine, collidine or quinoline.

The abovementioned compounds, which contain centres of asymmetry, can be used in the form of mixtures of isomers, especially of racemates, or in the form of pure isomers, especially of optically active antipodes.

The invention relates in particular to pharmaceutical preparations which contain a beta - receptor - blocking compound, viz. one of those mentioned above, together with a compound which regulates the thrombocyte - function, viz. one of those mentioned above, and optionally an alpha - receptor - bolcking compound, viz. one of those mentioned above, as well as the manufacture of these preparations, which can be used for the prophylactic and therapeutic treatment of coronary heart diseases, such as angina pectoris, coronary insufficiency or cardiac infarction.

The invention relates in particular to the new pharmaceutical preparations which contain 3 - isopropylamino - 1 - (1 - naphthyloxy) - 2 - propanol, 3 - isopropylamino - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - (2 - allyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (4 - acetylamino - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol, 3 - isopropylamino - 1 - [4 - (2 - methylthioethoxy) - phenoxy] - 2 - propanol, 1 - [2 - (3,4 - dimethoxyphenyl) - ethylamino] - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - isopropylamino - 3 - (1,2,3,4 - tetrahydro - 1,4 - ethano - 5 - naphthyloxy) - 2 - propanol, 1 - tert. - butylamino - 3 - (1,2,3,4 - tetrahydro - 2,3 - dihydroxy - 5 - naphthyloxy) - 2 - propanol, 1 - (7 - indenyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (7 - indanyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (5 - methyl - 8 - cumaryloxy) - 3 - isopropylamino - 2 - propanol, or 4 - (3 - isopropylamino - 2 - hydroxy - 1 - propyloxy) - 2 - methyl - indole, or above all, 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component and 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4.8 - di - piperidino - pyrimido[5,4 - d] - pyrimidine, or an acid addition salt thereof which can be used pharmaceutically, but especially 1 - (4 - hydroxy - phenyl) - 2 - phenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine or, above all, 1,2 - diphenyl - 4 - (2 - phenylsulphinylethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte - function, as well as 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, or an acid addition salt thereof which can be used pharmaceutically, as the alpha - receptor - blocking component which is optionally added.

The invention relates above all to the new pharmaceutical preparations which contain 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and

1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte - function, and which can optionally contain 2 - [N - (3 - hydroxyphenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, or an acid addition salt thereof which can be used pharmaceutically, as the alpha - receptor - blocking component, and which, because of their low degree of side effects, are particularly suitable for the treatment of coronary heart diseases.

Further preferred pharmaceutical preparations according to the present invention are those which contain 3 - isopropylamino - 1 - [4 - (2 - methoxy - ethyl) - phenoxy] - 2 - propanol, or an acid addition salt thereof which can be pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function, or which contain 3 - isopropylamino - 1 - (3 - methylphenoxy) - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 2,6 - bis [di - (2 - hydroxy - ethyl) -amino] - 4,8 - di - piperidinopyrimido[5,4 - d]-pyrimidine, or an acid addition salt thereof which can be used pharmaceutically, as the component which regulates the thrombocyte function, or which contain 1 - (4 - indolyl-oxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and O - acetyl - salicylic acid, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function, or which contain 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinylethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function.

A further subject of the present invention is the use, for the treatment of coronary heart diseases, of pharmaceutical preparations which contain a beta - receptor - blocking compound, such as one of the abovementioned compounds, especially one of the compounds with this type of action designated above as being preferred, above all 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol or an acid addition salt thereof which can be used pharmaceutically, and a compound which regulates the thrombocyte function, such as one of the abovementioned compounds, especially one of the compounds with this type of action designated above as being preferred, above all 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, and optionally, an alpha - receptor - blocking compound, such as one of the abovementioned compounds, especially one of the compounds with this type of action designated above as being preferred, above all 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methylphenyl) - aminomethyl] - 2 - imidazoline, or an acid addition salt thereof which can be used pharmaceutically, as the pharmaceutical active components.

Further pharmaceutical preparations which may be mentioned as being preferably suitable, within the scope of the present invention, for the treatment of coronary heart diseases are those which contain 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function, or those which contain 3 - isopropylamino - 1 - (3 - methylphenoxy) - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino-pyrimido[5,4 - d]pyrimidine, or an acid addition salt thereof which can be used pharmaceutically, as the component which regulates the thrombocyte function, or those which contain 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and O - acetylsalicylic acid, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function, or which contain 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function.

In the new pharmaceutical preparations, the ratio of the beta - receptor - blocking compound to the compound which regulates the thrombocyte function, as well as to the alpha - receptor - blocking compound which is optionally present, can vary within wide limits. In general, a ratio of about 1 : 1 to about 1 : 50 (by weight)

of the beta - receptor - blocking active compound to the active compound which regulates the thrombocyte function, especially an active compound of the type of the structural formula III, and a ratio of about 1:0.1 to 1:1 (by weight) of the beta - receptor - blocking active compound to the alpha - receptor - blocking active compound, which is optionally present, are preferred.

The absolute dosage of the active components in the new pharmaceutical preparations also varies greatly and depends, above all, on the individual degree of response to the active components to be used according to the invention. In general, the new preparations contain from about 0.002 g to about 0.3 g, preferably from about 0.005 g to about 0.2 g, of the beta-receptor-blocking active compound and from about 0.2 g to about 1.0 g, preferably from about 0.4 g to about 0.8 g, of an active compound which regulates the thrombocyte function, especially of an active compound of the structural formula III, and optionally from about 0.005 g to about 0.2 g, preferably from about 0.01 g to about 0.1 g, of an alpha - receptor - blocking active compound.

Thus, the preferred pharmaceutical preparations contain from about 0.02 g to about 0.25 g, preferably from 0.04 g to about 0.2 g, of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.2 g to about 1.0 g, preferably from about 0.4 g to about 0.8 g, of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or of a salt thereof with a base, which can be used pharmaceutically, and optionally, about 0.005 g to about 0.2 g, preferably from about 0.01 g to about 0.1 g, of 2 - [N - (3 - hydroxyphenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, or of an acid addition salt thereof which can be used pharmaceutically.

Further preferred pharmaceutical preparations according to the present invention contain from about 0.02 g to about 0.25 g, preferably from 0.05 g to about 0.150 g, of 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.2 g to about 1.0 g, preferably from about 0.4 g to about 0.8 g, of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or of a salt thereof with a base, which can be used pharmaceutically, or from about 0.050 g to about 0.250 g, preferably from about 0.060 g to about 0.150 g, of 3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.020 g to about 0.2 g, preferably from about 0.050 g to about 0.150 g, of 2,6 - bis - [di - (2 - hydroxyethyl) -amino] - 4,8 - di - piperidino - pyrimido[5,4 - d] - pyrimidine, or of an acid addition salt thereof which can be used pharmaceutically, or from about 0.005 g to about 0.080 g, preferably from about 0.015 g to about 0.050 g, of 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.7 g to about 2.0 g, preferably from about 1.0 g to about 1.5 g, of O - acetyl - salicylic acid, or of a pharmaceutically acceptable salt thereof with a base, or from about 0.005 g to about 0.080 g, preferably from about 0.015 g to about 0.050 g, of 1 - (4 - indolyloxy) - 3 - isopropylamino - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.1 g to about 1.0 g, preferably from about 0.2 g to about 0.8 g, of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or of a pharmaceutically acceptable salt thereof with a base.

In addition to the pharmacological active compounds, the new pharmaceutical preparations usually contain suitable excipients and auxiliaries which facilitate processing of the active compound to give the preparations which can be used pharmaceutically.

Preferably, the preparations, above all preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragées and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 20% to 100%, preferably from about 50% to about 90%, of active compound together with the excipient.

The pharmaceutical preparations of the present invention are manufactured in a manner which is in itself known, for example by means of conventional mixing, granulating, dragée - making, dissolving or lyophilising processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally granulating a resulting mixture and processing the mixture or granulates, after adding suitable auxiliaries if desired or necessary, to give tablets or dragée cores.

Suitable excipients are, in particular, fillers, such as sugars, for example lactose or sucrose, mannitol, or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as starch paste using, for example, maize starch, wheat starch, rice starch or potato starch, gelatine, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or if desired, disintegrating agents, such as the

abovementioned starches, and also carboxymethyl - starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings, which, if desired, are resistant to gastric juices, and for this purpose, inter alia, concentrated sugar solutions, which optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, in order to manufacture coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, are used. The period of action of one or more components which in themselves have actions of short duration can be prolonged by incorporating one or more active compounds into a suitable excipient which effects slow release of the active compound or active compounds. Dyestuffs or pigments can be added to the tablets or dragée coatings, for example for identification or in order to characterise different combinations of active compound doses.

Other pharmaceutical preparations which can be used orally are push-fit capsules made of gelatine, as well as soft, sealed capsules made of gelatine and a plasticiser, such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules, for example mixed with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, optionally, stabilisers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin or liquid polyethylene glycols, it also being possible to add stabilisers.

Possible pharmaceutical preparations which can be used rectally are, for example, suppositories, which consist of a combination of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. In addition, it is also possible to use gelatine rectal capsules which consist of a combination of the active compounds with a base; possible base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable formulations for parenteral administration are, above all, aqueous solutions of the active compounds in a water-soluble form, for example in the form of water-soluble salts, and also suspensions of the active compounds, such as appropriate 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 suspensions, which contain substances which increase the viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also contain stabilisers.

The examples which follow illustrate the invention described above; however, they are not intended to restrict the scope of the invention in any way.

Example 1:

Lacquer-coated tablets containing 0.08 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride and 0.3 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine can be manufactured as follows:

Composition (for one tablet)	
1 - (2 - allyloxy -phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride	0.080 g
1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine	0.300 g
maize starch	0.088 g
colloidal silica	0.020 g
magnesium stearate	0.002 g
stearic acid	0.005 g
sodium carboxymethyl starch	0.025 g
water	q.s.

The lacquer-coated tablets are manufactured as follows (for 10,000 tablets):

A mixture of 800 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride, 3,000 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, 300 g of maize starch and 200 g of colloidal silica is worked into a moist mass with a starch paste consisting of 450 g of maize starch and 2.2 kg of demineralised water. This mass is forced through a sieve of 3 mm mesh width and dried at 45°C for 30 minutes in a fluidised bed drier. The dry granules are pressed through a sieve of 1 mm mesh width and mixed with a previously sieved mixture (1 mm sieve) of 130 g of maize starch, 20 g of magnesium stearate, 50 g of stearic acid and 250 g of sodium carboxymethyl - starch and the mixture is pressed to give slightly domed tablets 11.5 mm in diameter.

The tablets which can be manufactured according to the above process are provided with a lacquer coating as follows:

The pressed tablets are coated, in a dragée-coating kettle 45 cm in diameter, with a solution of 20 g of shellac and 40 g of hydroxypropylmethylcellulose (low viscosity) in 110 g of methanol and 1,350 g of methylene chloride, by spraying evenly with the solution

in the course of 30 minutes; the coating is dried by blowing in air at 60°C at the same time.

Example 2:

Lacquer-coated tablets containing 0.16 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride and 0.4 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine can be manufactured as follows:

Composition (for one tablet):

1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride	0.160 g
1,2 - diphenyl - 3 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine	0.400 g
maize starch	0.120 g
colloidal silica	0.030 g
magnesium stearate	0.003 g
stearic acid	0.007 g
sodium carboxymethyl - starch	0.035 g
water	q.s.

The lacquer-coated tablets are manufactured as follows (for 20,000 tablets):

A mixture of 3,200 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride, 8,000 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, 750 g of maize starch and 600 g of colloidal silica is worked into a moist mass with a starch paste consisting of 1,250 g of maize starch and 6.4 kg of demineralised water. This mass is forced through a sieve of 3 mm mesh width and dried at 45°C for 30 minutes in a fluidised bed drier. The dry granules are forced through a sieve of 1 mm mesh width and mixed with a previously sieved mixture (1 mm sieve) of 400 g of maize starch, 60 g of magnesium stearate, 140 g of stearic acid and 700 g of sodium carboxymethyl - starch and the mixture is pressed to give domed tablets in the shape of small rods 16.4 mm in length and 8.6 mm in width.

The lacquer coating is applied to the tablets, thus obtainable, as follows:

5,000 of the above pressed tablets are coated, in a dragée-coating kettle 45 cm in diameter, with a solution of 20 g of shellac and 40 g of hydroxypropylmethylcellulose (low viscosity) in 110 g of methanol and 1,350 g of methylene chloride by spraying continuously with the solution in the course of 30 minutes; the coating is dried by blowing in warm air at 60°C at the same time.

Example 3:

Punctiform tablets containing 0.08 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride, 0.3 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine and 0.05 g of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride, the latter being in a form suitable for slow release, are manufactured as follows:

Composition of tablets suitable for the slow release of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride (for 1 tablet):

2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride	0.0500 g
hydroxypropylmethylcellulose (low viscosity)	0.0015 g
hydrogenated cottonseed oil	0.0050 g
magnesium stearate	0.0005 g

The tablets containing 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride are manufactured as follows (for 10,000 tablets):

A mixture of 500 g of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride and 15 g of hydroxypropylmethylcellulose is worked into a moist mass with 150 g of demineralised water and this mass is granulated through a sieve of 3 mm mesh width, dried at 45°C for 30 minutes and comminuted through a 0.6—0.8 mm sieve. After admixing 50 g of hydrogenated cottonseed oil in pulverulent form and 5 g of magnesium stearate, the mass is pressed to give sightly domed tablets 6 mm in diameter.

The punctiform tablets which additionally contain 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are manufactured as follows:

The granules described in Example 1 are processed to tablets and the tablet, described above, for the slow release of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride is pressed into the former pressed tablet in such a way that one surface of the tablet which is pressed in is visible from the outside. A highly domed press tool 11.5 mm in diameter is used for the outer cover, which has a weight of 0.520 g.

Example 4:

Punctiform dragées containing 0.08 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride, 0.3 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine and 0.05 g of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 -

imidazoline hydrochloride, the latter being in a form suitable for slow release, are manufactured as follows:

5,000 g of tablets obtainable according to the process described in Example 3 are placed in a dragée-coating kettle 45 cm in diameter and provided with a protective lacquer consisting of a dispersion of 350 g of a copolymer of acrylic acid ethyl ester and methacrylic acid methyl ester (70:30) in demineralised water containing 105 g of lactose and 105 g of talc. This protective lacquer is sprayed on continuously for 30 minutes and dried at the same time with warm air at 60°C. The increase in weight is about 0.01 g. The cores which have been lacquer-coated in this way, are further coated with a sugar solution. For this purpose a sugar syrup consisting of two parts of sugar and one part of water, with the addition of talc (18%), polyvinylpyrrolidone (1.5%) and polyethylene glycol 6000 (1%), is first used until the weight of the tablets has increased by about 0.145 g and a pure sugar syrup is then used until a final dragée weight of about 0.890 g is reached.

Example 5:

Punctiform tablets containing 0.08 g of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride, 0.3 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine and 0.1 g of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride, the latter being in a form suitable for slow release, are manufactured as follows:

Composition of tablets suitable for the slow release of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride (for 1 tablet):	
2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride	0.100 g
hydroxypropylmethylcellulose (low viscosity)	0.003 g
hydrogenated cottonseed oil	0.010 g
magnesium stearate	0.001 g

The tablets containing 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline hydrochloride and the punctiform tablets which additionally contain 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol hydrochloride and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are manufactured according to the process described in Example 3. The punctiform tablets can be converted into punctiform dragées by the process described in Example 4.

Example 6:

Capsules containing 0.1 g of 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol tartarate and 0.4 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine can be manufactured as follows:

Composition (for one capsule)	
3 - isopropylamino 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol tartarate	0.1 g
1,2 - diphenyl - 4 - (2 - phenyl - sulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine	0.4 g
colloidal silica	0.013 g
hydroxypropylmethyl cellulose (low viscosity)	0.042 g
gelatine	0.012 g
magnesium stearate	0.006 g
polyvinylpyrrolidone	0.007 g

The capsules are manufactured as follows (for 10,000 capsules):

A mixture of 1,000 g of 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol tartarate and 80 g of colloidal silica is sieved through a sieve with a mesh width of 1.6 mm and granulated, in a fluidised bed, with an aqueous solution of 70 g of polyvinylpyrrolidone and the granules are then dried at 40°C. 4,000 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are moistened with an aqueous solution of 120 g of gelatine, dried and converted into a granular state by means of extrusion and the granules are dried at 45°C. The two lots of dried granules are combined and mixed with 420 g of hydroxypropylmethylcellulose, 50 g of colloidal silica and 60 g of magnesium stearate and the mixture is filled, by machine, into 10,000 capsules of size 000.

Example 7:

Dragées containing 0.075 g of 3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol hydrochloride and 0.1 g of 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]pyrimidine are manufactured as follows:

Composition (for one dragée):	
3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol hydrochloride	0.075 g
2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]pyrimidine	0.1 g
magnesium stearate	0.003 g
maize starch	0.085 g
polyvinylpyrrolidone	0.009 g

The dragées are manufactured as follows (for 10,000 dragées):

A mixture of 750 g of 3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol hydrochloride, 1,000 g of 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]pyrimidine, 830 g of lactose and 550 g of maize starch is moistened with an aqueous solution of 90 g of polyvinylpyrrolidone, the moist mixture is kneaded and granulated and the granules are dried at 45°C. The dried granules are forced through a sieve with a mesh width of 1.2 mm and mixed with 300 g of maize starch and 30 g of magnesium stearate and the mixture is pressed to give 10,000 dragée cores. These are coated with a sugar coating in the customary way.

Example 8:

Tablets containing 0.020 g of 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol and 1.0 g of O - acetylsalicylic acid are manufactured as follows:

Composition (for one tablet):

1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol	0.020 g
O - acetylsalicylic acid	1.0 g
rice starch	0.1 g

The tablets are manufactured as follows (for 5,000 tablets):

A mixture of 100 g of 1 - (4 - indolyloxy) - 3 - isopropyl - amino - 2 - propanol and 500 g of rice starch is forced through a sieve with a mesh width of 0.5 mm. 5,000.0 g of crystalline O - acetylsalicylic acid are added to this mixture and the whole is mixed well. The mixture is then pressed to give 5,000 tablets.

Example 9:

Capsules containing 0.020 g of 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol and 0.4 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are manufactured as follows:

Composition (for one capsule):

1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol	0.020 g
1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine	0.4 g
gelatine	0.015 g
magnesium stearate	0.005 g
maize starch	0.060 g

The capsules are manufactured as follows (for 10,000 capsules):

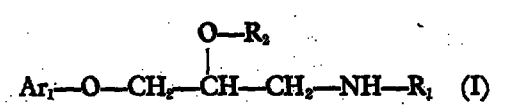
A mixture of 200 g of 1 - (4 - indolyloxy) - 3 - isopropyl - amino - 2 - propanol and 400 g of maize starch is forced through a sieve with a mesh width of 0.5 mm, 100 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are added and the whole is mixed. A further 3,000 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are added to this mixture and the whole is mixed well. The mixture is then moistened with an aqueous solution of 150 g of gelatine, kneaded and converted to a granular state by means of extrusion and the granules are dried at 45°C. 200 g of maize starch and 50 g of magnesium stearate are added to the dried granules and the mixture is filled. by machine, into 10,000 capsules of size 00.

Example 10:

In the above Examples 1—9 it is possible to use 3 - isopropylamino - 1 - (1 - naphthyloxy) - 2 - propanol, 1 - (2 - allyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (4 - acetylamino - phenoxy) - 3 - isopropylamino - 2 - propanol, 3 - isopropylamino - 1 - [4 - (2 - methylthioethoxy) - phenoxy] - 2 - propanol, 1 - [2 - (3,4 - dimethoxyphenyl) - ethylamino] - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - isopropylamino - 3 - (1,2,3,4 - tetrahydro - 1,4 - ethano - 5 - naphthyloxy) - 2 - propanol, 1 - tert. - butylamino - 3 - (1,2,3,4 - tetrahydro - 2,3 - dihydroxy - 5 - naphthyloxy) - 2 - propanol, 1 - (7 - indenyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (7 - indanyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (5 - methyl - 8 - cumaryloxy) - 3 - isopropylamino - 2 - propanol, 4 - (3 - isopropylamino - 2 - hydroxy - 1 - propyloxy) - 2 - methyl - indole or 2 - tert. - butylamino - 1 - (7 - ethyl - 2 - benzofuranyloxy) - ethanol, preferably in the form of an acid addition salt which can be used pharmaceutically, such as the hydrochloride, in place of the active compounds used in these examples as the beta - receptor - blocking component.

WHAT WE CLAIM IS:—

1. Pharmaceutical preparations for the prophylactic and therapeutic treatment of coronary heart diseases which contain, (1) a beta - receptor - blocking compound which is a compound of the formula



wherein Ar_1 represents a monocyclic or polycyclic, carbocyclic or heterocyclic radical which contains at least one ring of aromatic character, and which is bonded to the oxygen atom via a ring carbon atom, preferably of the ring of aromatic character, R_1 denotes an optionally substituted aliphatic, cycloaliphatic or araliphatic hydrocarbon radical and R_2 presents hydrogen or the acyl radical of

The dragées are manufactured as follows (for 10,000 dragées):

A mixture of 750 g of 3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol hydrochloride, 1,000 g of 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]pyrimidine, 830 g of lactose and 550 g of maize starch is moistened with an aqueous solution of 90 g of polyvinylpyrrolidone, the moist mixture is kneaded and granulated and the granules are dried at 45°C. The dried granules are forced through a sieve with a mesh width of 1.2 mm and mixed with 300 g of maize starch and 30 g of magnesium stearate and the mixture is pressed to give 10,000 dragée cores. These are coated with a sugar coating in the customary way.

Example 8:

Tablets containing 0.020 g of 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol and 1.0 g of O - acetylsalicylic acid are manufactured as follows:

Composition (for one tablet):

1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol	0.020 g
O - acetylsalicylic acid	1.0 g
rice starch	0.1 g

The tablets are manufactured as follows (for 5,000 tablets):

A mixture of 100 g of 1 - (4 - indolyloxy) - 3 - isopropyl - amino - 2 - propanol and 500 g of rice starch is forced through a sieve with a mesh width of 0.5 mm. 5,000.0 g of crystalline O - acetylsalicylic acid are added to this mixture and the whole is mixed well. The mixture is then pressed to give 5,000 tablets.

Example 9:

Capsules containing 0.020 g of 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol and 0.4 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are manufactured as follows:

Composition (for one capsule):

1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol	0.020 g
1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine	0.4 g
gelatine	0.015 g
magnesium stearate	0.005 g
maize starch	0.060 g

The capsules are manufactured as follows (for 10,000 capsules):

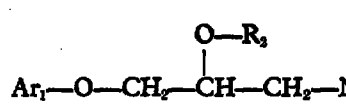
A mixture of 200 g of 1 - (4 - indolyloxy) - 3 - isopropyl - amino - 2 - propanol and 400 g of maize starch is forced through a sieve with a mesh width of 0.5 mm, 100 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are added and the whole is mixed. A further 3,000 g of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine are added to this mixture and the whole is mixed well. The mixture is then moistened with an aqueous solution of 150 g of gelatine, kneaded and converted to a granular state by means of extrusion and the granules are dried at 45°C. 200 g of maize starch and 50 g of magnesium stearate are added to the dried granules and the mixture is filled. by machine, into 10,000 capsules of size 00.

Example 10:

In the above Examples 1—9 it is possible to use 3 - isopropylamino - 1 - (1 - naphthyloxy) - 2 - propanol, 1 - (2 - allyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (4 - acetylamino - phenoxy) - 3 - isopropylamino - 2 - propanol, 3 - isopropylamino - 1 - [4 - (2 - methylthioethoxy) - phenoxy] - 2 - propanol, 1 - [2 - (3,4 - dimethoxyphenyl) - ethylamino] - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - isopropylamino - 3 - (1,2,3,4 - tetrahydro - 1,4 - ethano - 5 - naphthyloxy) - 2 - propanol, 1 - tert. - butylamino - 3 - (1,2,3,4 - tetrahydro - 2,3 - dihydroxy - 5 - naphthyloxy) - 2 - propanol, 1 - (7 - indenyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (7 - indanyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (5 - methyl - 8 - cumaryloxy) - 3 - isopropylamino - 2 - propanol, 4 - (3 - isopropylamino - 2 - hydroxy - 1 - propyloxy) - 2 - methyl - indole or 2 - tert. - butylamino - 1 - (7 - ethyl - 2 - benzofuranyloxy) - ethanol, preferably in the form of an acid addition salt which can be used pharmaceutically, such as the hydrochloride, in place of the active compounds used in these examples as the beta - receptor - blocking component.

WHAT WE CLAIM IS:—

1. Pharmaceutical preparations for the prophylactic and therapeutic treatment of coronary heart diseases which contain, (1) a beta - receptor - blocking compound which is a compound of the formula

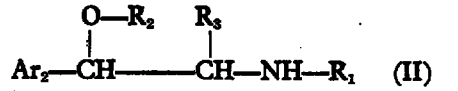


$$Ar_1—O—CH_2—\underset{\displaystyle O—R_2}{\underset{|}{CH}}—CH_2—NH—R_1 \quad (I)$$

wherein Ar_1 represents a monocyclic or polycyclic, carbocyclic or heterocyclic radical which contains at least one ring of aromatic character, and which is bonded to the oxygen atom via a ring carbon atom, preferably of the ring of aromatic character, R_1 denotes an optionally substituted aliphatic, cycloaliphatic or araliphatic hydrocarbon radical and R_2 represents hydrogen or the acyl radical of an

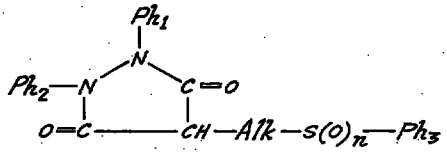
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organic carboxylic acid, or a compound of the formula



(II)

wherein R_1 and R_2 have the abovementioned meanings, Ar_2 represents a monocyclic or polycyclic, carbocyclic radical which contains at laest one ring of aromatic character, and R_3 denotes hydrogen or lower alkyl, or a salt of such compounds which can be used pharmaceutically, (2) a compound which regulates the thrombocyte function which is O - acetyl - salicylic acid, or a salt thereof with a base, which can be used pharmaceutically, 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]-pyrimidine, or an acid addition salt thereof which can be used pharmaceutically, or a compound of the formula



(III)

wherein each of the radicals Ph_1 and Ph_2 independently of one another represents a phenyl radical which is optionally substituted by lower alkyl, hydroxyl, lower alkoxy and/or halogen, Alk denotes a lower alkylene radical which separates the sulphur atom from the ring carbon atom by at least 2 carbon atoms, n represents 0, 1 or 2 and Ph_3 represents a phenyl radical which is optionally substituted by lower alkyl, lower alkoxy and/or halogen, or a salt thereof with a base, which can be used pharmacologically, and optionally, (3), an alpha - receptor - blocking compound which is a hydrogenated ergot alkaloid, or a mixture of such alkaloids or acid addition salts thereof which can be used pharmaceutically, or a N - benzyl - N - halogeno - lower alkylamine, a 2 - tert. - aminomethyl - benzodioxane, a N - substituted dibenzazepine or a methyl - 2 - imidazoline which is substituted in the 2 - position, or acid addition salts of such compounds which can be used pharmaceutically.

2. Pharmaceutical preparations according to Claim 1, characterised in that these contain 3 - isopropylamino - 1 - (1 -naphthyloxy) - 2 - propanol, 3 - isopropylamino - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - (2 - allyl - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (4 - acetylamino - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol, 3 - isopropylamino - 1 -[4 - (2 - methylthioethoxy) - phenoxy] - 2 - propanol, 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, 1 - [2 - (3,4 - dimethylphenyl) - ethylamino] - 3 - (3 - methyl - phenoxy) - 2 - propanol, 1 - isopropylamino - 3 - (1,2,3,4 - tetrahydro - 1,4 - ethano - 5 - naphthyloxy) - 2 - propanol, 1 - tert. - butylamino - 3 - (1,2,3,4 - tetrahydro - 2,3 - dihydroxy - 5 - naphthyloxy) - 2 - propanol, 1 - (7 - indenyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (7 - indanyloxy) - 3 - isopropylamino - 2 - propanol, 1 - (5 - methyl - 8 - cumaryloxy) - 3 - isopropylamino - 2 - propanol, or 4 - (3 - isopropylamino - 2 - hydroxy - 1 - propyloxy) - 2 - methyl - indole, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]pyrimidine, or an acid addition salt thereof which can be used pharmaceutically, 1 - (4 - hydroxy - phenyl) - 2 - phenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine or 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function, and 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, or an acid addition salt thereof which can be used pharmaceutically, as the alpha - receptor - blocking component which is optionally added.

3. Pharmaceutical preparations according to Claim 1, characterised in that these contain 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte - function.

4. Pharmaceutical preparations according to Claim 4, characterised in that these contain 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, or an acid addition salt thereof which can be used pharmaceutically, as the alpha - receptor - blocking component which is optionally added.

5. Pharmaceutical preparations according to Claim 1, characterised in that these contain 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the

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component which regulates the thrombocyte function.

6. Pharmaceutical preparations according to Claim 1, characterised in that these contain 3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido-[5,4 - d]pyrimidine, or an acid addition salt thereof which can be used pharmaceutically, as the component which regulates the thrombocyte function.

7. Pharmaceutical preparations according to Claim 1, characterised in that these contain 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and O - acetylsalicylic acid, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function.

8. Pharmaceutical preparations according to Claim 1, characterised in that these contain 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or an acid addition salt thereof which can be used pharmaceutically, as the beta - receptor - blocking component, and 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or a salt thereof with a base, which can be used pharmaceutically, as the component which regulates the thrombocyte function.

9. Pharmaceutical preparations according to one of Claims 1—8, characterised in that the ratio of the beta - receptor - blocking active compound to the active compound which regulates the thrombocyte function, particularly an active compound of the type of the structural formula III, is about 1:1 to about 1:50 (ratio by weight) and the ratio of the beta - receptor - blocking active compound to the alpha - receptor - blocking active compound, which is optionally present, is about 1:0.1 to about 1:1 (ratio by weight).

10. Pharmaceutical preparations according to one of Claims 1—8, characterised in that these contain from about 0.002 g to about 0.3 g, preferably from about 0.005 g to about 0.2 g, of the beta - receptor - blocking active compound and from about 0.2 g to about 1.0 g, preferably from about 0.4 g to about 0.8 g, of an active compound which regulates the thrombocyte function, especially an active compound of the structural formula III, and, optionally, from about 0.005 g to about 0.2 g, preferably from about 0.01 g to about 0.1 g, of an alpha - receptor - blocking active compound.

11. Pharmaceutical preparations according to Claim 3 or 4, characterised in that these contain from about 0.02 g to about 0.25 g, preferably from about 0.04 g to about 0.2 g, of 1 - (2 - allyloxy - phenoxy) - 3 - isopropylamino - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.2 g to about 1.0 g, preferably from about 0.4 g to about 0.8 g, of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - diozo - pyrazolidine, or of a salt thereof with a base, which can be used pharmaceutically, and, optionally, from about 0.005 g to about 0.2 g, preferably from about 0.01 g to about 0.1 g, of 2 - [N - (3 - hydroxy - phenyl) - N - (4 - methyl - phenyl) - aminomethyl] - 2 - imidazoline, or of an acid addition salt thereof which can be used pharmaceutically.

12. Pharmaceutical preparations according to Claim 5 characterised in that these contain from about 0.02 g to about 0.25 g, preferably from 0.05 g to about 0.150 g, of 3 - isopropylamino - 1 - [4 - (2 - methoxyethyl) - phenoxy] - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.2 g to about 1.0 g, preferably from about 0.4 g to about 0.8 g, of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or of a salt thereof with a base, which can be used pharmaceutically.

13. Pharmaceutical preparations according to Claim 6, characterised in that these contain from about 0.050 g to about 0.250 g, preferably from 0.060 g to about 0.150 g, of 3 - isopropylamino - 1 - (3 - methyl - phenoxy) - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.020 g to about 0.2, preferably from about 0.050 g to about 0.150 g, of 2,6 - bis - [di - (2 - hydroxyethyl) - amino] - 4,8 - di - piperidino - pyrimido[5,4 - d]-pyrimidine, or of an acid addition salt thereof which can be used pharmaceutically.

14. Pharmaceutical preparations according to Claim 7, characterised in that these contain from about 0.005 g to about 0.080 g, preferably from about 0.015 g to about 0.050 g, of 1 - (4 - indolyloxy) - 3 - isopropylamino - 2 - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.7 g to about 2.0 g, preferably from about 1.0 g to about 1.5 g, of O - acetylsalicylic acid, or of a pharmaceutically acceptable salt thereof with a base.

15. Pharmaceutical preparations according to Claim 8, characterised in that these contain from about 0.005 g to about 0.080 g, preferably from about 0.015 g to about 0.050 g, of 1 - (4 - indolyloxy) - 3 - isopropylamino - propanol, or of an acid addition salt thereof which can be used pharmaceutically, and from about 0.1 g to about 1.0 g, preferably from about 0.2 g to about 0.8 g, of 1,2 - diphenyl - 4 - (2 - phenylsulphinyl - ethyl) - 3,5 - dioxo - pyrazolidine, or of a pharmaceutically acceptable salt thereof with a base.

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16. Preparations according to one of Claims 1—15, which can be administered orally.

17. Pharmaceutical preparations according to claim 1 as hereinbefore described in examples 1—10.

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