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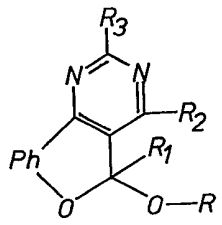
(54) Benzopyranopyrimidines

(57) Benzopyranopyrimidines, many of which are novel, of the formula I



(I),

in which

Ph represents an optionally substituted 1,2-phenylene radical,

R represents a lower aliphatic hydrocarbon radical optionally substituted by a Ph_1 radical, Ph_1 being an optionally substituted phenyl radical, or a C_{3-1} cycloalkyl radical, a lower alkyl radical substituted by a heteroaromatic radical, or radical of the formula

$$(CH_2CH_2O)_n—CH_2CH_2OR_4$$

in which *n* is 0, 1 or 2 and R_4 represents hydrogen or lower alkyl,

each of the symbols R_1 and R_2 represents hydrogen or lower alkyl,

R_3 represents an optionally substituted phenyl radical Ph_1, a lower alkyl radical optionally substituted by Ph_1, a C_{3-7} cycloalkyl radical, a cycloalkyl-Ph_1 radical in which cycloalkyl and Ph_1 have the meanings given above, or a heteroaromatic radical,

and therapeutically acceptable salts of these compounds, have *lipid-reducing, anti-arteriosclerotic* and *analgesic* actions.

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The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

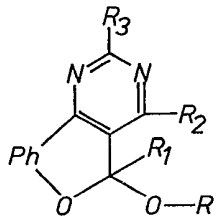
Pharmaceutical Preparations Containing Substituted Ether Compounds, Their Use, Novel Substituted Ether Compounds, and Processes for Their Manufacture

The invention relates to pharmaceutical preparations containing substituted ethers of 5-hydroxy-5H[1]benzopyrano-[4,3-d]pyrimidines and their therapeutic use.

In Liebigs Ann. Chem. 1976, p. 1663—1673, U. Petersen and H. Heitzer describe the reaction of 4-oxo-4H-chromene-3-carbaldehydes with amidines, in which 5-hydroxy-5H-[1]benzo-pyrano[4,3-d]pyrimidine compounds are obtained. Furthermore, in Arch. Pharm. (Weinheim), *310*, page 559—563 (1977), W. Löwe discloses the perchlorate of 5-ethoxy-2,5-dimethyl-5H-[1]benzopyrano[4,3-d]pyrimidine. A pharmacological action of those compounds, however, is not described.

Surprisingly, it has now been found that the substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines have valuable pharmacological actions.

The invention therefore relates especially to pharmaceutical preparations containing substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines of the general formula I



(I),

in which

Ph represents an optionally substituted 1,2-phenylene radical,

R represents a lower aliphatic hydrocarbon radical optionally substituted by a Ph_1 radical, Ph_1 being an optionally substituted phenyl radical, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a lower alkyl radical substituted by a heterocyclic radical of aromatic character, or a radical of the formula $(CH_2CH_2O)_n—CH_2CH_2OR_4$ in which *n* has the value 0, 1 or 2 and R_4 represents hydrogen or lower alkyl,

each of the symbols R_1 and R_2 represents hydrogen or lower alkyl,

R_3 represents an optionally substituted phenyl radical Ph_1, a lower alkyl radical optionally substituted by Ph_1, a cycloalkyl radical containing from 3 to 7 carbon atoms, a cycloalkyl-Ph_1 radical in which cycloalkyl and Ph_1 have the meanings given above, or a heterocyclic radical of aromatic character, and therapeutically acceptable salts of these compounds.

The term "lower" in the organic radicals and compounds mentioned hereinbefore and hereinafter denotes those having not more than 7, preferably 4, and especially 1 or 2, carbon atoms.

Hereinbefore and hereinafter the general terms may have the following meanings:

An optionally substituted 1,2-phenylene radical Ph can be substituted, for example, by one, two or three identical or different substituents. Such substituents are, for example, hydroxy, lower alkyl, hydroxy-lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonyl-lower alkyl, halogen, halo-lower alkyl, trifluoromethyl, nitro or amino and, in addition, in two adjacent positions, an anellated 1,2-cycloalkylene or 1,2-phenylene radical.

An optionally substituted phenyl radical Ph_1 can be substitued by one, two or three identical or different substituents. Such substituents are, for example, hydroxy, lower alkyl, hydroxy-lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonyl-lower alkyl, halogen, halo-lower alkyl, trifluoromethyl, nitro or amino.

A lower aliphatic hydrocarbon radical is a lower alkyl, lower alkenyl or lower alkynyl radical.

Lower alkyl groups are, for example, methyl and ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl or n-heptyl groups.

In the hydroxy-lower alkyl groups, for example the lower alkyl groups mentioned above are substituted in any position by hydroxy.

Lower alkenyl groups are, for example, the allyl or the 2-methylallyl group and lower alkynyl groups are preferably propargyl groups.

A lower alkoxycarbonyl group is, for example, the methoxycarbonyl or ethoxycarbonyl group.

A lower alkoxycarbonyl-lower alkyl group is, for example, the methoxycarbonylmethyl group or the ethoxycarbonylmethyl group.

A cycloalkyl group is, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group.

A heterocyclic radical of aromatic character is preferably monocyclic, such as pyrryl, for example 2-pyrryl or 3-pyrryl, pyridyl, for example 2-, 3- or 4-pyridyl, also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl.

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

Halogen atoms are especially fluorine, chlorine or bromine atoms, but may alternatively be iodine atoms.

Halo-lower alkyl groups have the halogen atom at any position of a lower alkyl radical.

The basic compounds of the general formula I form acid addition salts. In the preparations of the invention, therapeutically acceptable, non-toxic acid addition salts are used. For their manufacture there are used, for example, inorganic acids, for example hydrochloric or hydrobromic acid, or sulphuric, phosphoric, nitric or perchloric acid; or organic acids, such as carboxylic or sulphonic acids, for example formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, pamoic, nicotinic, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic, benzenesulphonic, halobenzenesulphonic, toluenesulphonic, naphthalenesulphonic, sulphanilic or cyclohexylsulphamic acid; or ascorbic acid. On the other hand, compounds that contain at least one phenolic hydroxy group form metal salts, especially alkali metal salts or alkaline earth metal salts, for example sodium or potassium salts. In the preparations, therapeutically acceptable, non-toxic, metal salts are used.

The compounds used in the preparations of the invention have valuable pharmacological properties, for example hypolipidaemic actions together with a favourable influence on the lipoprotein spectrum and, furthermore, especially compounds of the formula I in which R_3 represents a heterocyclic radical of aromatic character, especially pyridyl, analgesic effects. These pharmacological properties can be demonstrated in animal experiments, preferably on mammals, for example rats. For this, the compounds can be administered enterally or parenterally, preferably orally, subcutaneously or intraperitoneally, in a dosage range of from 1 to 100 mg/kg/day. For example, the reduction of low and very low density lipoproteins (LDL and VLDL) and also the reduction of cholesterol and triglycerides in the serum is determined as follows: 50 mg of active substance are administered perorally once daily to male rats on three days. On the 4th day, the animals are treated twice. On the 5th day, serum is obtained and the lipoproteins are separated by an ultracentrifuge. In the serum and in the isolated lipoprotein fractions the cholesterol and triglycerides are determined. [K. R. Müller and R. G. Cortesi, Artery 4 (6): 564—577 (1978)].

The analgesic action can be demonstrated, for example, in rats in the case of oral administration of doses of 1 mg/kg and above.

The preparations containing the above-mentioned compounds can therefore be used as lipid-reducing agents and anti-arteriosclerotics or analgesics.

Preferred pharmaceutical preparations contain compounds of the formula I in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, hydroxy-lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonyl-lower alkyl, halogen, halo-lower alkyl, trifluoromethyl, nitro or amino, R represents lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 7 carbon atoms, Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, or represents a lower alkyl radical substituted by a pyrryl, pyridyl or thienyl radical, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents a phenyl radical Ph_1 defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents a pyrryl, pyridyl or thienyl radical, and therapeutically acceptable salts of these compounds.

Especially preferred pharmaceutical preparations contain compounds of the formula I in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, lower alkoxy, lower alkoxycarbonyl-lower alkyl, halogen or trifluoromethyl, R represents lower alkyl or Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, each of the symbols R_1 and R_2 represents lower alkyl, or preferably hydrogen, R_3 represents a phenyl radical Ph_1 as defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents pyridyl, and therapeutically acceptable salts of these compounds.

Prominence should be given to those pharmaceutical preparations which contain compounds of the formula I in which Ph represents the 1,2-phenylene radical, R represents lower alkyl or phenyl-lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents lower alkyl, phenyl, lower alkoxy-phenyl, phenyl-lower alkyl or pyridyl, and therapeutically acceptable salts of these compounds.

Special prominence should be given to those pharmaceutical preparations which contain compounds of the formula I in which Ph represents the 1,2-phenylene radical, R represents lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents the phenyl radical optionally substituted by lower alkoxy, and therapeutically acceptable salts of these compounds.

The invention relates also to novel substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines and processes for their manufacture.

The invention relates especially to novel substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines of the general formula I given above in which Ph represents an optionally substituted 1,2-phenylene radical, R represents a lower aliphatic hydrocarbon radical optionally substituted by a Ph_1 radical, Ph_1 being an optionally substituted phenyl radical, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a lower alkyl radical substituted by a heterocyclic radical of aromatic character, or a radical of the formula $(CH_2CH_2O)_n—CH_2CH_2OR_4$ in which *n* has the value 0, 1 or 2 and R_4 represents

hydrogen or lower alkyl, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents an optionally substituted phenyl radical Ph_1, a lower alkyl radical optionally substituted by Ph_1, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a cycloalkyl-Ph_1 radical, wherein cycloalkyl and Ph_1 have the meanings given above, or a heterocyclic radical of aromatic character, and their salts, especially therapeutically acceptable salts, of these compounds, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof.

The meaning of the general terms has already been given above.

The free basic compounds of the formula I can be converted into corresponding acid addition salts with inorganic or organic acids, especially with those mentioned above, which produce therapeutically acceptable acid addition salts. On the other hand, compounds having a free phenolic hydroxy group can be converted into their alkali metal salts, for example with alkali metal hydroxide solutions.

The novel compounds exhibit the pharmacological actions mentioned above. They can therefore be used as lipid-reducing agents and anti-arteriosclerotics or analgesics. They can also be used as intermediates for the manufacture of other valuable compounds or preparations, especially pharmacologically active compounds or preparations.

Preferred compounds are those of the formula I in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, hydroxy-lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonyl-lower alkyl, halogen, halo-lower alkyl, trifluoromethyl, nitro or amino, R represents lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 7 carbon atoms, Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, or a lower alkyl radical substituted by a pyrryl, pyridyl or thienyl radical, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents a phenyl radical Ph_1 defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents a pyrryl, pyridyl or thienyl radical, and salts, especially therapeutically acceptable salts, of these compounds, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof.

Especially preferred are compounds of the formula I in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, lower alkoxy, lower alkoxycarbonyl-lower alkyl, halogen or trifluoromethyl, R represents lower alkyl or Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, each of the symbols R_1 and R_2 represents lower alkyl, or preferably hydrogen, R_3 represents a phenyl radical Ph_1 as defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents pyridyl, and salts, especially therapeutically acceptable salts of these compounds, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof.

Prominence should be given to those compounds of the formula I in which Ph represents the 1,2-phenylene radical, R represents lower alkyl or phenyl-lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents lower alkyl, phenyl, lower alkoxyphenyl, phenyl-lower alkyl or pyridyl, and salts, especially therapeutically acceptable salts, of these compounds.

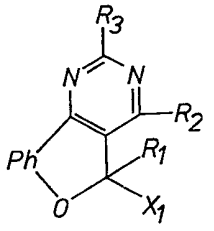
Special prominence should be given to those compounds of the formula I in which Ph represents the 1,2-phenylene radical, R represents lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents the phenyl radical optionally substituted by lower alkoxy, and salts, especially therapeutically acceptable salts, of these compounds.

The invention relates especially to the novel compounds described in the Examples and their salts, especially therapeutically acceptable salts, of these compounds.

The compounds of the present invention are obtained according to processes known *per se*.

The novel compounds of the formula I are manufactured, for example, by

(a) etherifying a compound of the general formula II with a compound of the general formula III

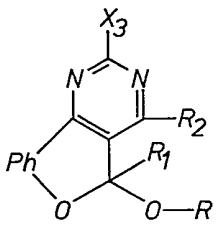


(II)

with X_2-R (III)

in which one of the radicals X_1 and X_2 represents a free, metallated or reactive esterified hydroxy group and the other respectively represents a free, reactive esterified or metallated hydroxy group, or X_2 together with the radical R in the compound X_2-R represents a compound that introduces the radical R if X_1 represents a free hydroxy group, or

(b) a compound of the general formula IV

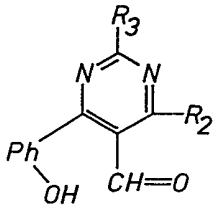


(IV),

in which X_3 represents a group that can be split off, is condensed with an organometallic compound of the formula R_3-M in which M represents a metallic grouping, or with an R_3-halide in the presence of a metal, and, if desired, a resulting compound of the formula I is converted into a different compound according to the invention, and/or, if desired, a resulting free compound is converted into a salt or a salt is converted into the free compound or into a different salt, and/or, if desired, a resulting mixture of isomers or racemates is separated into the individual isomers or racemates, and/or, if desired, resulting racemates are split into the optical antipodes.

If X_2-R represents a compound that introduces the radical R, it may be a corresponding diazo compound, an acetal corresponding to the alcohol ROH, or a corresponding orthoester, a corresponding oxonium, carbenium or halonium salt or a corresponding triazene compound.

If R_1 in the formula II represents hydrogen and X_1 represents the free hydroxy group, this starting material may alternatively be in the tautomeric form of the formula IIa



(IIa)

If each of the two substituents X_1 and X_2 in the starting materials of the formulae II and III represents a free hydroxy group, the reaction is carried out in the presence of proton donors, i.e. with acid catalysis. As proton donors there are used, especially, strong inorganic acids or organic sulphonic acids, for example mineral acids, such as hydrohalic acids, for example hydrochloric acid, also sulphuric acid, or for example, *p*-toluenesulphonic acid, or alternatively Lewis acids, such as halides of boron, aluminium or zinc, for example boron trifluoride, aluminium chloride or zinc chloride. Etherification is carried out preferably without the addition of solvent, in the corresponding alcoholic solution, i.e. in an alcohol of the formula ROH, provided that the latter is in liquid form at the temperature at which the reaction is carried out.

If one of the radicals X_1 and X_2 is a free or metallated hydroxy group, preferably a hydroxy group metallated by an alkali metal atom, for example ONa, then the other radical is in the form of a reactive esterified hydroxy group. A reactive esterified hydroxy group is preferably a hydroxy group esterified by a strong mineral or sulphonic acid, such as a hydrohalic, sulphuric, lower alkanesulphonic or benzenesulphonic acid, for example hydrochloric, hydrobromic, methanesulphonic, trifluoromethanesulphonic, benzenesulphonic or *p*-toluenesulphonic acid. Such esters are, *inter alia*, lower alkyl halides, di-lower alkyl sulphates, such as dimethyl sulphate, or fluorosulphonic acid esters, such as lower alkyl esters, for example fluorosulphonic acid methyl ester, or optionally halogen-substituted methanesulphonic acid lower alkyl esters, for example trifluoromethanesulphonic acid methyl ester. The hydroxy group of the starting material of the formula II or III can, however, alternatively be esterified by, for example, a lower alkanoic acid, such as acetic acid or propionic acid. If one of the radicals X_1 or X_2 represents the free hydroxy group, etherification is carried out in the presence of basic condensation agents which bind the acids formed. Such agents are alkaline earth or alkali metal carbonates or bicarbonates, for example calcium or sodium carbonates or bicarbonates, or tertiary amines, for example tri-lower alkylamines, pyridines or lower alkylated pyridines. If one of the starting materials is used in the form of the metallated compound (for example, X_1=ONa), the reaction is carried out under neutral conditions. Finally, if, for example, the hydroxy group X_1 is in the form of a hydroxy group esterified by a lower alkanoic acid, for example acetic acid, the reaction can be carried out with a corresponding alcohol ROH in an acidic medium, preferably in the presence of a mineral acid, for example a hydrohalic acid, such as hydrochloric acid. The reactions are, if necessary, carried out with the addition of an inert solvent, such as an optionally halogenated, such as chlorinated, aliphatic, cycloaliphatic or aromatic hydrocarbon, for example methylene chloride, an ether, such as dioxan or tetrahydrofuran, or a mixture of these solvents.

The etherification reaction described above can be considerably accelerated by phase-transfer catalysis [see Dehmlow, Angewandte Chemie, vol. 5, p. 187 (1974)]. As phase-transfer catalysts there may be used quaternary phosphonium salts and especially quaternary ammonium salts, such as optionally substituted tetraalkylammonium halides, for example tetrabutylammonium chloride, bromide or iodide, or alternatively benzyltriethylammonium chloride, in catalytic or up to equimolar amounts. Any solvent that is not miscible with water can be used as the organic phase, for example one of the optionally halogenated, such as chlorinated, lower aliphatic, cycloaliphatic or aromatic hydrocarbons, such as tri- or tetra-chloroethylene, tetrachloroethane, carbon tetrachloride, chlorobenzene, toluene or xylene. Suitable as condensation agents are alkali metal carbonates or bicarbonates, for example potassium or sodium carbonate or bicarbonate, alkali metal phosphates, for example potassium phosphate, and alkali metal hydroxides, for example sodium hydroxide.

The starting materials of the formula II in which X_1 represents the free hydroxy group can also be etherified, as already mentioned above, by reaction with corresponding diazo compounds. Such compounds are, for example, diazo-lower alkanes, such as diazomethane, diazoethane, diazo-n-butane, or alternatively Ph_1-diazo-lower alkanes, for example phenyl-diazomethane. These reagents are used in the presence of a suitable inert solvent, such as an aliphatic, cycloaliphatic or aromatic hydrocarbon, such as hexane, cyclohexane, benzene or toluene, a halogenated aliphatic hydrocarbon, for example methylene chloride, or an ether, such as a di-lower alkyl ether, for example diethyl ether, or a cyclic ether, for example tetrahydrofuran or dioxan, or a solvent mixture, and, depending on the diazo reagent, while cooling, at room temperature or while heating slightly, and, if necessary, in a closed vessel and/or under an inert gas atmosphere, for example a nitrogen atmosphere.

If X_1 represents hydroxy, further etherifying agents are suitable acetal compounds, for example *gem*-di-lower alkoxy-lower alkanes, such as 2,2-dimethoxypropane, which are used in the presence of strong organic sulphonic acids, such as *p*-toluenesulphonic acid, and a suitable solvent, such as a di-lower alkyl sulphoxide or lower alkylene sulphoxide, for example dimethyl sulphoxide, or suitable orthoesters, for example orthoformic acid tri-lower alkyl esters, for example orthoformic acid triethyl ester, which are used in the presence of a strong mineral acid, for example sulphuric acid, or a strong organic sulphonic acid, such as *p*-toluenesulphonic acid, and a suitable solvent, such as an ether, for example dioxan.

If X_1 represents the free hydroxy group, further etherifying agents are corresponding tri-substituted oxonium salts (so-called Meerwein salts) or di-substituted carbenium or halonium salts in which the substituents are the etherifying radicals R, for example tri-lower alkyloxonium salts, and di-lower alkoxycarbenium or di-lower alkylhalonium salts, especially the corresponding salts with complex, fluorine-containing acids, such as the corresponding tetrafluoroborates, hexafluorophosphates, hexafluoroantimonates or hexachloroantimonates. Such reagents are, for example, trimethyloxonium or triethyloxonium hexafluoroantimonate, hexachloroantimonate, hexafluorophosphate or tetrafluoroborate, dimethoxycarbenium hexafluorophosphate or dimethylbromonium hexafluoroantimonate. These etherifying agents are preferably used in an inert solvent, such as an ether or a halogenated hydrocarbon, for example diethyl ether, tetrahydrofuran or methylene chloride, or in a mixture thereof, if necessary in the presence of a base, such as an organic base, for example a preferably sterically hindered tri-lower alkylamine, for example N,N-diisopropyl-N-ethylamine, and while cooling, at room temperature or while heating slightly, for example at from approximately −20°C to approximately 50°C, if necessary in a closed vessel and/or under an inert gas atmosphere, for example a nitrogen atmosphere.

If the substituent X_1 of the starting material of the formula II is a free hydroxyl group, further etherifying agents are, finally, corresponding 1-substituted 3-aryltriazene compounds in which the substituent is the etherifying radical R, and aryl represents preferably optionally substituted phenyl, for example lower alkylphenyl, such as 4-methylphenyl. Such triazene compounds are 3-aryl-1-lower alkyltriazenes, for example 3-(4-methylphenyl)-1-methyltriazene, 3-(4-methylphenyl)-1-ethyltriazene or 3-(4-methylphenyl)-1isopropyltriazene. These reagents are usually used in the presence of inert solvents, such as optionally halogenated hydrocarbons or ethers, for example benzene, or solvent mixtures, and while cooling, at room temperature and preferably at elevated temperature, for example at from approximately 20°C to approximately 100°C, if necessary in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

In the starting materials of process variant b), the group X_3 which can be split off is, for example, the radical of a strong inorganic acid, such as a hydrohalic acid, for example hydrochloric, hydrobromic or hydriodic acid, i.e. a chlorine, bromine or iodine atom, or of sulphuric acid, or of an organic sulphonic acid, preferably a lower alkanesulphonic acid, for example methylsulphonyl or ethylsulphonyl. In the compounds of the formula R_3-M, the metallic grouping M is preferably an alkaline earth or alkali metal atom for example a calcium, magnesium, sodium, potassium or lithium atom. Metals used in the condensation reaction are especially alkaline earth metals, but more especially alkali metals, for example sodium or potassium. Heavy metals, such as, for example, copper, may, however, also be used. The reaction is preferably carried out in the presence of inert solvents, especially in aromatic hydrocarbons, for example benzene or toluene or in an ether, for example diethyl ether.

If a free phenolic hydroxy group is present, the agents and/or conditions chosen for carrying out

the etherification according to the process are those which selectively etherify only the hydroxy group in the 5-position of the starting material, such as, for example, treatment under relatively mild conditions with the relevant alcohol in an acidic medium.

In resulting compounds, substituents can be modified within the scope of the definition of the end products. For example, in a product of the formula I, the substituent R can be exchanged for a different substituent R, for example by treating with a different alcohol of the formula ROH, optionally in the presence of an acid. If a product contains a phenolic hydroxy group, the latter can be converted into a lower alkoxy group in known manner, for example by reacting with a diazo-lower alkane or by reacting with a lower alkyl halide, such as iodide or bromide, for example in the presence of silver oxide or silver carbonate. If a nitro group is present in a 1,2-phenylene radical Ph or in a phenyl radical Ph_1, it can be replaced by a lower alkoxy group, such as methoxy or ethoxy, in known manner, for example by treating with an alkali metal lower alkoxide, such as sodium methoxide or sodium ethoxide, preferably in an anhydrous lower alkanol, for example methanol or ethanol. A nitro group can also be converted into the amino group in known manner, for example with catalytically activated hydrogen.

Acid addition salts of compounds of the formula I are obtained in customary manner, for example by treating with an acid or a suitable anion exchanger. The resulting salts can be converted into the free compounds in a manner known *per se*, for example by treating with a suitable basic agent, for example a metal hydroxide, ammonia or a hydroxyl ion exchanger. On the other hand, compounds having a phenolic hydroxy group can be converted into an alkali metal salt in a manner known *per se* by treating, for example, with an alkali metal hydroxide. The free compounds can be obtained by treating with an acid.

The therapeutically acceptable salts mentioned above are preferred. These or other salts, for example the picarates, can also be used in the purification of free bases. The bases are converted in to their salts, the salts are separated and the base are liberated from the salts. Owing to the close relationships between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter there shall optionally be understood by free compounds and salts, where appropriate with regard to meaning and purpose, also the corresponding salts and free compounds, respectively.

Starting materials and end products that are isomeric mixtures can be separated into the individual isomers by methods known *per se*, for example by fractional distillation, crystallisation and/or chromatography. Racemic products can be separated into the optical antipodes, for example by chromatography and/or separation of their diastereoisomeric salts, for example by fractional crystallisation of the d- or l-camphor-sulphonates, -mandelates, -tartrates or -dibenzoyltartrates.

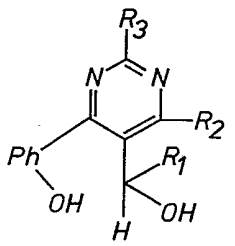
The invention relates also to modifications of the present process, according to which an intermediate obtainable at any stage of the process is used as starting material and the remaining process steps are carried out, or the process is discontinued at any stage, or according to which a starting material is formed under the reaction conditions, or in which a starting material is used in the form of a salt or a reactive derivative. The invention also comprises novel intermediates resulting therefrom.

In the process of the present invention the starting materials used are preferably those which result in the compounds described at the beginning as being especially valuable.

The starting materials used in the process for the manufacture of the compounds of the present invention are known or, if they are novel, they can be manufactured by methods known *per se*, for example in a manner analogous to that described in the Examples. The invention relates also to novel starting materials.

The known starting materials of the formula II in which X_1 represents hydroxy are described in Liebigs Annalen der Chemie, 1976, p. 1663—1673 and in Arch. Pharm. (Weinheim) *310*, p. 559—563 (1977) by the authors mentioned above.

A further manufacturing method for the starting materials of the formula II consists of the oxidation of compounds of the general formula V



(V),

in which R_1 represents hydrogen, optionally while temporarily protecting the phenolic hydroxy group.

As oxidising agents there can be used, for example, dimethyl sulphoxide and acetic anhydride, N-chlorosuccinimide and dimethyl sulphide (Corey), chromic acid and sulphuric acid in water at low temperatures, or the method according to Oppenauer (aluminium tert.-butoxide, acetone and benzene and splitting off by solvolysis, for example with dilute sulphuric acid). If the phenolic hydroxy group is protected for example by a tert.-butyl group, then it is also freed *in situ*.

A starting material of the formula II in which X_1 represents a metallated hydroxy group can be manufactured, for example, by reacting the corresponding free compound (X_1=OH) with an alkali metal, for example sodium or potassium, in the presence of an inert solvent, for example an ether, such as diethyl ether, or an aromatic hydrocarbon, for example benzene.

A starting material of the formula II in which X_1 represents an esterified hydroxy group, for example a halogen atom or an acyloxy group, such as an acetoxy, methanesulphonyloxy or benzenesulphonyloxy group, can be obtained starting from the corresponding compound in which X_1 represents hydroxy. Esterification can be carried out in a manner known *per se*.

The conversion of the free hydroxy group X_1 into a hydroxy group esterified by a hydrohalic acid, i.e. into a halogen atom, can be carried out in the usual manner by treating with a halogenating, especially chlorinating, agent. Such agents are, for example, thionyl chloride, thionyl bromide, phosphorus tribromide, phosphorus oxybromide or oxychloride or phosphorus pentachloride, which are usually used in the presence of an inert solvent or diluent, for example tetrahydrofuran, dioxan, methylene chloride or dimethyl sulphoxide.

A hydroxy group X_1 of the starting material of the formula II can be converted into an acyloxy group X_1 for example by treating with an acylating agent that introduces the desired acyl radical of an organic carboxylic acid. Such agents are, for example, corresponding carboxylic acids or their reactive derivatives, such as anhydrides or acid halides, for example chlorides or bromides. The reaction can optionally be carried out in the presence of condensation agents, for example in the presence of carbodiimide compounds, such as dicyclohexylcarbodiimide, or carbonyl compounds, such as diimidazolylcarbonyl, when using free carboxylic acids. When using acid derivatives, for example acid halides, the reaction is carried out advantageously in the presence of a basic agent, for example a tri-lower alkylamine, such as triethylamine, or a heterocyclic base, for example pyridine.

If the substituent X_1 in a starting material of the formula II represents sulphonyloxy, it can be manufactured starting from a corresponding compound in which X_1 represents hydroxy. Thus, the hydroxy compound can be converted into the desired starting material by treatment with a reactive sulphonic acid derivative, such as a corresponding halide, for example chloride, if necessary in the presence of a basic agent for neutralising the acid formed. The compounds mentioned above in connection with the manufacture of carboxylic acid esters can be used as basic agents.

Starting materials of the formula III in which X_2 represents a metallated, or a reactive esterified, hydroxy group can be manufactured analogously to the method described for the compounds of the formula II, starting from alcohols of the formula ROH.

The starting materials of the formula IV of process b) can be manufactured as follows: the precursor of the starting material, which contains a free amino group in the 2-position, is obtained analogously to the method described in Liebigs Ann. Chem. *1976*, p. 1663—1673, by reacting corresponding chromone-2-carbaldehydes with guanidine. The conversion of the amino group into a halogen atom can be carried out, for example, by converting into a diazonium salt and reacting with a copper(I) halide.

The above-mentioned reactions are carried out according to methods known *per se*, in the presence or absence of diluents, preferably in those which are inert towards, and dissolve, the reactants, and in the presence or absence of catalysts, condensation agents or neutralising agents and/or in an inert atmosphere, while cooling, at room temperature or at elevated temperatures. preferably at the boiling point of the solvent used, at normal or elevated pressure.

The invention also comprises therapeutic compositions that consist of an amount of compounds of the general formula I having a lipid-reducing or analgesic action or a salt and a pharmacologically acceptable solid carrier or liquid diluent.

The pharmaceutical preparations according to the invention contain at least one compound of the general formula I or a salt thereof as the active substance together with a customary pharmaceutical carrier. The type of carrier depends largely on the field of use. The pharmaceutical compositions according to the invention which contain, as active substances, compounds of the formula I can be administered orally, parenterally or rectally.

For oral treatment there come into consideration, especially, solid unit dosage forms, such as tablets, dragées and capsules, which preferably contain between 10 and 90% of an active substance of the general formula I or a salt in order to allow administration to warm-blooded animals of daily doses of from 1 to 50 mg/kg. For the manufacture of tablets and dragée cores, the compounds of the general formula I are combined with solid, pulverulent carriers, such as lactose, saccharose, sorbitol, maize starch, potato starch or amylopectin, cellulose derivatives or gelatine, preferably with the addition of lubricants, such as magnesium or calcium stearate, or polyethylene glycols of a suitable molecular weight. Dragée cores are subsequently coated, for example with concentrated sugar solutions which may contain, in addition, gum arabic, talc and/or titanium dioxide, or with a lacquer dissolved in readily volatile organic solvents or solvent mixtures. Colouring substances can be added to these coatings, for example for indicating different doses of active substance. Soft gelatine capsules and other closed capsules consist, for example, of a mixture of gelatine and glycerin and may contain, for example, mixtures of a compound of the formula I and polyethylene glycol. Dry-filled capsules contain, for example, granules of an active substance with solid, pulverulent carriers, such as, for example, lactose,

saccharose, sorbitol, mannitol; starches, such as potato starch, maize starch or amylopectin, cellulose derivatives and gelatine and also magnesium stearate or stearic acid.

Unit dosage forms that come into consideration for rectal administration are, for example, suppositories which consist of a combination of an active substance with a suppository base based on natural or synthetic triglycerides (for example cocoa butter), polyethylene glycols or suitable higher fatty alcohols, and gelatine rectal capsules which contain a combination of the active substance with polyethylene glycols.

Ampoule solutions for parenteral administration, especially for intramuscular or intravenous administration, contain a compound of the formula I or a salt thereof in a concentration of preferably 0.5 to 5% as an aqueous dispersion prepared with the aid of customary solubilisers and/or emulsifiers, and, optionally, stabilisers, or preferably as an aqueous solution of a pharmaceutically acceptable water-soluble salt of a compound of the general formula I.

The concentration of the active substance for liquids that are to be taken orally, such as syrups or elixirs, is so selected that a single dose can easily be measured, for example as the contents of a teaspoon or a measuring spoon of, for example, 5 ml, or also as a multiple of that volume.

The following Examples a) to c) are intended to illustrate the manufacture of some typical forms of administration, but do not in any way represent the only embodiments of those forms of administration.

a) 250 g of active substance are mixed with 550 g of lactose and 292 g of potato starch, and the mixture is moistened with an alcoholic solution of 8 g of gelatine and granulated by being passed through a sieve. After drying, 60 g of talc, 10 g of magnesium stearate and 20 g of colloidal silica are added and the mixture is pressed to form 10,000 tablets each weighing 119 mg and each containing 25 mg of active substance, which may, if desired, be provided with dividing notches for a finer adjustment of the dosage.

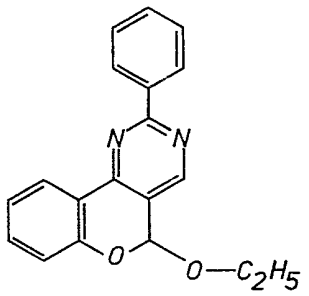
b) A granulate is prepared from 100 g of active substance, 379 g of lactose and the alcoholic solution of 6 g of gelatine, which, after being dried, is mixed with 10 g of colloidal silica, 40 g of talc, 60 g of potato starch and 5 g of magnesium stearate and pressed to form 10,000 dragée cores. These are subsequently coated with a concentrated syrup consisting of 533.5 g of cryst. saccharose, 20 g of shellac, 75 g of gum arabic, 250 g of talc, 20 g of colloidal silica and 1.5 g of colouring substance, and dried. The resulting dragées each weigh 150 mg and each contain 10 mg of active substance.

c) 25 g of active substance and 1975 g of finely ground suppository base (for example, cocoa butter) are thoroughly mixed and then melted. 1000 suppositories of 2 g are cast from the melt which has been kept homogeneous by stirring. They each contain 25 mg of active substance.

The following Examples serve to illustrate the invention but are not intended to limit the scope thereof in any way. Temperatures are given in degrees Centigrade and data regarding parts relate to parts by weight. Unless defined otherwise, the evaporation of solvents is carried out under reduced pressure, for example between approximately 0.1 and 15 mm Hg.

Example 1

A solution of 8 g of 2-phenyl-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine and 5 ml of 10N ethanolic hydrochloric acid in 200 ml of ethanol is boiled under reflux, with the exclusion of water, for 2 hours. The reaction mixture is then evaporated to dryness under reduced pressure, ice and 20 ml of saturated aqueous sodium carbonate solution are added and the mixture is extracted three times with diethyl ether. The ether extracts are dried over sodium sulphate and concentrated by evaporation under reduced pressure. The residue is recrystallised from pentane. 2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine of the formula



is obtained which melts at 79—80°.

Example 2

3.3 g of conc. sulphuric acid are added to a solution of 8 g of 2-phenyl-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 300 ml of methanol and the mixture is boiled under reflux, with the exclusion of water, for 5-1/2 hours. The reaction mixture is then adjusted to pH 8 with 0.5N aqueous sodium hydroxide solution while cooling with ice and extracted with ethyl acetate and diethyl ether.

The organic extracts are dried over sodium sulphate and concentrated by evaporation under reduced pressure. The residue is recrystallised from benzene/diethyl ether. 2-phenyl-5-methoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 142—143°.

Example 3

Analogously to the process described in Example 2, starting from 2-phenyl-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine and the corresponding alkanol [1) propanol, 2) butanol, 3) isopropanol, 4) pentanol, 5) hexanol], the following 2-phenyl-5-alkoxy-5H-[1]benzopyrano[4,3-d]pyrimidine compounds are obtained:

1) 2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine. Extracted with dichloroethane. m.p. 68—69° after recrystallisation from propanol.

2) 2-phenyl-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine. Extracted with dichloroethane. m.p. 66—69° (from butanol).

3) 2-phenyl-5-isopropoxy-5H-[1]benzopyrano[4,3-d]pyrimidine. Extracted with dichloroethane. m.p. 90—92° (from isopropanol).

4) 2-phenyl-5-pentyloxy-5H-[1]benzopyrano[4,3-d]pyrimidine. Extracted with dichloroethane. m.p. 69—70° (from pentane).

5) 2-phenyl-5-hexyloxy-5H-[1]benzopyrano[4,3-d]pyrimidine. Extracted with dichloroethane. m.p. 69—70° (from pentane).

Example 4

Analogously to the process described in Example 2, starting from 10 g of 8,9-trimethylene-2-phenyl-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, 8,9-trimethylene-2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 135—136° after recrystallisation from diethyl ether.

The starting material is obtained according to the process described in Ann. Chem., *1976*, 1663, starting from 6,7-trimethylene-4H-4-oxo-[1]benzopyran-3-carboxaldehyde [described in German Offenlegungsschrift 751 211; Pat. No. 2,523,194; Haas *et al.*, Ciba-Geigy AG] and benzamidine. 8,9-trimethylene-2-phenyl-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine melts at 213—214° (recrystallised from ethanol).

Example 5

Analogously to the process described in Example 4, the following compounds are obtained starting from the corresponding hydroxy compounds and ethanol:

a) 8,9-tetramethylene-2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine which, after recrystallisation from diethyl ether and then from benzine, melts at 142—145°,

b) 8-phenyl-11-ethoxy-11H-naphtho[1′,2′;7,8]pyrano[4,3-d]pyrimidine which, after recrystallisation from ethyl acetate/diethyl ether, melts at 151 to 153°.

The starting materials can easily be manufactured starting from the aldehydes described in German Offenlegungsschrift 2,523,194 (cf. Example 4):

starting material for a): 8,9-tetramethylene-2-phenyl-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 213—214° (from ethanol)

starting material for b): 8-phenyl-11-hydroxy-11-naphtho-[1′,2′;7,8]pyrano[4,3-d]pyrimidine, m.p. 224—227° (from ethanol).

Example 6

Analogously to the process described in Example 2, there are obtained, starting from the 2-R_3-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines correspondingly substituted in the 2-position, the following 2-R_3-5-OR-5H-[1]-benzopyrano[4,3-d]pyrimidines of the formula I in which the phenylene radical Ph is unsubstituted, R_1 and R_2 represent hydrogen and the other symbols have the following meanings:

compound	R_3	*R*	*extracted with*	*lised from*	*m.p.*
1	2-pyridyl	ethyl	dichloro-ethane	diethyl ether	140—141°
2	4-pyridyl	propyl	dichloro-ethane	diethyl ether	115—116°
3	3-pyridyl	ethyl	diethyl ether/ethyl acetate	diethyl ether/ ethyl acetate	98—100°
4	3-methoxy-phenyl	propyl	dichloro-ethane	diethyl ether/ pentane	72—73°
5	4-cyclo-hexylphenyl	propyl	—	propanol	99—100°
6	4-chloro-phenyl	propyl	—	propanol	101°
7	3-methyl-phenyl	propyl	dichloro-ethane	pentane	86°
8	4-ethoxy-carbonyl-methylphenyl	ethyl	diethyl ether/ ethyl acetate	dichloro-ethane/ diethyl ether	115°

The 2-R_3-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines used as starting materials are manufactured analogously to the process described in Ann. Chem., *1976*, 1663, starting from 4-oxo-4H-[1]benzopyran-3-carboxaldehyde and the corresponding amidine of the formula R_3—$CNHNH_2$:

	starting material: R_3:	*recrystallisation from:*	*m.p.:*
1	2-pyridyl	ethanol/water	220°
2	4-pyridyl	ethanol/water	275—280°
3	3-pyridyl	ethanol/water	270—275°
4	3-methoxyphenyl	ethanol/water	168—169.5°
5	4-cyclohexylphenyl	ethanol/water	188—190°
6	4-chlorophenyl	ethanol/water	208—210°
7	3-methylphenyl	ethanol/water	167—168°
8	4-ethoxycarbonyl methylphenyl	ethanol/water	112—115°

Example 7

6 g of *p*-toluenesulphonic acid are added to a solution of 8 g of 2-(4-pyridyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 200 ml of n-propanol and the mixture is boiled under reflux for 3 hours. The reaction mixture is then concentrated by evaporation under reduced pressure to a volume of approximately 50 ml and, thereby, crystalline 2-(4-pyridyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine tosylate is obtained which melts at 188—190°.

Example 8

Analogously to the process described in Example 2, the following compounds are obtained starting from corresponding 5-hydroxy compounds and propanol and isopropanol, respectively:

1) 8,9-dimethyl-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine which, after recrystallisation from propanol, melts at 167—168°.

2) 9-ethyl-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 82—83° (from pentane).

3) 7-methyl-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 100—101° (from propanol).

4) 9-chloro-2-phenyl-5-propoxy-5H- [1]benzopyrano[4,3-d]pyrimidine, m.p. 122—123° (from propanol).

5) 9-chloro-2-phenyl-5-isopropoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 149—150° (from pentane).

The corresponding 5-hydroxy compounds used as starting materials have the following melting point

starting material:	*recrystallisation from:*	*m.p.:*
1)	ethanol/water	220—222°
2)	ethanol/water	178—179°
3)	ethanol/water	192—194°
4) and 5)	ethanol/water	199—201°

Example 9

117 g of 2-(4-methoxyphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine are boiled with 800 ml of n-propanol and 0.2 ml of conc. sulphuric acid under reflux for 2 hours, with the exclusion of water. The solution is then concentrated by evaporation to half its volume and the product is made to crystallise in a refrigerator at 0°. After filtering and washing with cold petroleum ether, 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 104—105°.

Example 10

Analogously to the process described in Example 9, the following compounds are obtained starting from the corresponding 5-hydroxy compound and n-propanol and n-butanol, respectively,

1) 2-methyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 48—49° (from pentane at —60°).

2) 2-(3,4-dimethoxybenzyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 73—75° (from propanol).

3) 2-(3,5-dimethoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 85—86° (from petroleum ether).

4) 2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 61—62° (from petroleum ether).

5) 2-(4-hydroxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 220° with decomposition (from ethyl acetate).

6) 2-phenyl-5-butoxy-9-chloro-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 120—122° (from methylene chloride/dimethyl ether).

7) 2-(5-methylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 76—78° (from butanol).

8) 2-(4-methoxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 82—84° (from butanol).

9) 2-(3-methoxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 60° (from pentane).

10) 2-(4-ethoxycarbonylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 91—92° (from petroleum ether).

11) 2-(4-ethoxycarbonylmethylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 80—82° (from petroleum ether).

The starting material used for the above compound 4), namely 2-(3-pyridyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, is manufactured according to the process described in Ann. Chem. *1976*, 1663, starting from 4-oxo-[1]benzopyran-3-carboxaldehyde and 3-pyridylamidine. m.p. 230° with decomposition (from ethanol).

Example 11

Analogously to the process described in Example 1, starting from 2-phenyl-5-methyl-5-hydroxy-[1]benzopyrano[4,3-d]pyrimidine and ethanol, 2-phenyl-5-methyl-5-ethoxy[1]benzopyrano[4,3-d]pyrimidine is obtained, the hydrochloride of which melts at 180°.

The starting material can be manufactured according to the process described in Ann. Chem. *1976,* 1663, starting from 3-acetylchromone and benzamidine. The 5-hydroxy compound melts at 240—245° after recrystallisation from ethanol.

Example 12

Analogously to the process described in Example 1, the following compounds also are obtained:

1) 2-(4-hydroxyphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine. m.p. 210° (from ethyl acetate).

2) 2-(4-methoxycarbonylphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine. m.p. 161—163° (from ethanol).

Example 13

Analogously to the process described in Example 7, the following compounds are obtained starting from the corresponding 5-hydroxy compounds and the respective alkanol:

1) 2-(3-pyridyl)-5-methoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 197—199° (recrystallised from methylene chloride/diethyl ether).

2) 2-(3-pyridyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 102—103° (from methylene chloride/diethyl ether).

3) 8-ethyl-2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 75—76° (from methylene chloride/diethyl ether).

4) 6-methyl-2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 99—100° (from diethyl ether/petroleum ether).

5) 2-(4-pyridyl)-5-methoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 179—180° (from methylene chloride/diethyl ether).

6) 2-(4-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 102—103° (from diethyl ether/petroleum ether).

The 2-R_3-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines which are used as starting materials and have not been mentioned in the preceding Examples are obtained analogously to the process described in Ann. Chem., *1976,* 1663, starting from correspondingly substituted 4-oxo-4H-[1]benzopyran-3-carboxaldehydes and the correspovding amidine R_3—$CNHNH_2$:

8-ethyl-2-(3-pyridyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 195° (from ethanol),

6-methyl-2-(3-pyridyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 245—247° (from ethanol).

Example 14

20 ml of isopropanol saturated with hydrogen chloride are added to a solution of 5 g of 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 50 ml of isopropanol and the mixture is left to stand overnight at room temperature. The crystallisate is filtered with suction, washed with ether and dried. 2-(4-methoxyphenyl)-5-isopropoxy-5H-[1]benzopyrano[4,3-d]pyrimidine hydrochloride is obtained which melts at 168—170°.

Example 15

A solution of 5 g of 2-(4-methoxyphenyl)-5-propionyloxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 100 ml of ethanol is boiled under reflux for one hour. Water is then added to the reaction mixture until it becomes cloudy, and it is left overnight to cool to room temperature. The crystallisate is filtered with suction, washed with a little ethanol and ether and dried. 2-(4-methoxyphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 106—108°.

The starting material is manufactured as follows:

1.45 ml of propionyl chloride are added dropwise to a solution of 5 g of 2-(4-methoxyphenyl)-5-hydroxy-5H-[1]-benzopyrano[4,3-d]pyrimidine in 50 ml of anhydrous tetrahydrofuran and 2.4 ml of triethylamine while stirring in an anhydrous atmosphere at —5°. The reaction mixture is then stirred for 2 hours at room temperature, poured onto water and extracted with ether. The combined organic phases are washed twice with water, dried over sodium sulphate and concentrated by evaporation under reduced pressure at 22°. The residue is recrystallised from methylene chloride/petroleum ether. 2-(4-methoxyphenyl)-5-propionyloxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 130—131°.

Example 16

Analogously to the process described in Example 2, the following is obtained starting from 2-(4-chloromethylphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine and propanol:

1) 2-(4-chloromethylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine which, after recrystallisation from n-propanol, melts at 103—104°; and,

starting from 2-(4-hydroxymethylphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3]pyrimidine and butanol;

2) 2-(hydroxymethylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 122—123° (from n-propanol).

The starting materials are manufactured analogously to Example 4, starting from 4H-4-oxo-[1]benzopyran-3-carboxaldehyde and the benzamidine that is substituted in the 4-position by chloromethyl and hydroxymethyl, respectively. There are obtained:

1a) 2-(4-chloromethylphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 169—170° (from ethanol) and

2a) 2-(4-hydroxymethylphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine, m.p. 200—201° (from ethanol).

Example 17

0.57 g of orthoformic acid triethyl ester and one drop of conc. sulphuric acid are added to a solution of 1.5 g of 2-(4-methoxyphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 50 ml of benzene and the mixture is boiled under reflux for 2 hours. The mixture is then evaporated to dryness, the residue is is partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution, the organic phase is washed twice with water, dried over sodium sulphate and evaporated to dryness under reduced pressure. The residue is recrystallised from methylene chloride/ether. 2-(4-methoxyphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 105—107°.

Example 18

2.25 g of 4-bromoanisole in 10 ml of absolute tetrahydrofuran are added dropwise, while stirring, in an anhydrous atmosphere, to a suspension of 361 mg of magnesium in a little absolute tetrahydrofuran. When the addition is complete, stirring is continued for 90 minutes at 60—70°. The reagent is cooled to room temperature and a solution of 3.20 g of 2-methylsulphonyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 20 ml of absolute tetrahydrofuran is added and stirring is then continued for 16 hours at room temperature. The reaction solution, which is then dark brown, is evaporated to dryness under reduced pressure. The residue is partitioned between three times 100 ml of chloroform and 100 ml of saturated aqueous ammonium chloride solution. The organic phases are washed neutral, dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. Purification of the resulting brown oil by chromatography over 120 g of silica gel using chloroform as eluant yields pure 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrao[4,3-d]pyrimidine. m.p. 102—104° (from n-propanol/petroleum ether).

The starting material is manufactured as follows:

1 ml of conc. sulphuric acid is added at 100°, while stirring, to 37 g of 2-methylthio-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 250 ml of n-propanol and the mixture is boiled under reflux for 2 hours. The mixture is then concentrated by evaporation to a volume of approximately 50 ml, cooled to 0° with ice and partitioned between ice-cold aqueous 2N sodium carbonate solution and methylene chloride. The organic phases are washed with water, dried over anhydrous sodium sulphate and concentrated by evaporation under reduced pressure until crystallisation begins. 2-methylthio-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 112—114°.

10.35 g of *m*-chloroperbenzoic acid (90%) are added in portions at room temperature to 7.2 g of the compound obtained above in 100 ml of absolute chloroform and the mixture is stirred overnight at room temperature with the exclusion of water. The reaction mixture is then partitioned between 200 ml of chloroform and two times 200 ml of saturated aqueous sodium bisulphite solution. The organic extracts are washed in succession with two times 200 ml of aqueous sodium bicarbonate solution and water, dried over anhydrous sodium sulphate and concentrated by evaporation under reduced pressure. 2-methylsulphonyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained from the evaporation residue with ether. m.p. 141—143°.

Example 19

1 g of 2-(4-methoxyphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine is added to a suspension of 160 mg of sodium hydride (50% in mineral oil) in 15 ml of absolute dimethylformamide and the mixture is stirred at room temperature until the evolution of hydrogen has ceased. 600 mg of propyl iodide are then added slowly and stirring is continued for 2 hours at 40—50°. The mixture is then poured onto 200 ml of ice-water and extracted three times with 50 ml of methylene chloride each time. The organic phases are washed with water, dried over sodium sulphate and concentrated by evaporation under reduced pressure. After distilling off the excess dimethylformamide in a high vacuum, the evaporation residue yields, after recrystallisation from n-propanol/ether, 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine which melts at 102—103°.

Example 20

In a manner analogous to that described in Example 19, there is obtained starting from 2-(4-hydroxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, after treatment with sodium hydride and methyl iodide, 2-(4-methoxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine which melts at 82—84°.

Example 21

A solution of 32 mg of sodium in 5 ml of absolute n-butanol is added to 350 mg of 2-(4-hydroxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 15 ml of absolute n-butanol. The solution, which is then yellow, is evaporated to dryness. The sodium salt of the above-mentioned compound is obtained in the form of a yellow powder which melts above 300°.

Example 22

A solution of 300 mg of sodium in 5 ml of absolute methanol is evaporated to dryness under

reduced pressure. A solution of 1 g of 2-(4-nitrophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 5 ml of absolute N,N-dimethylformamide is added to the residue under anhydrous conditions and the mixture is left to stand at room temperature for 24 hours. 100 ml of water are then added and the reaction mixture is extracted three times with 50 ml of ether each time. The organic phases are washed neutral, dried over sodium sulphate and evaporated to dryness under reduced pressure. Purification of the evaporation residue by chromatography over silica gel using chloroform as eluant and subsequent crystallisation from ethyl yield 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine. m.p. 97—100°.

The starting material is obtained starting from *p*-nitrobenzamidine and 3-formylchromone, with 2-(4-nitrophenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine (m.p. 220—222°) being obtained as intermediate. The treatment of that compound with sulphuric acid and n-propanol yields 2-(4-nitrophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine which melts at 160—162°. (This compound is also an end product of the invention).

Example 23

Analogously to the process described in Example 2, starting from 2-(3-trifluoromethylphenyl)-5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine (m.p. 205—207°; from ethanol/water) and n-propanol, 2-(3-trifluoromethylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which, after recrystallisation from n-propanol, melts at 117—118°.

Example 24

0.72 g of conc. sulphuric acid is added to a warm solution of 5 g of 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine in 60 ml of n-propanol. The mixture is then cooled to room temperature, 50 ml of ether are added and filtration is carried out. 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine hemisulphate is obtained which melts at 185°.

When methanesulphonic acid is used, the corresponding methanesulphonate which melts at 182—184° is obtained analogously.

The corresponding hydrochloride (m.p. 180°) is obtained using hydrochloric acid.

Example 25

A mixture of 5 g of 2-(4-nitrophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine, 50 ml of dioxan and 1 g of Raney nickel is hydrogenated at room temperature under normal pressure until 3 equivalents of hydrogen have been consumed. The catalyst is filtered off, the solution is concentrated by evaporation and the residue is recrystallised from ether/petroleum ether. 2-(4-aminophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine is obtained which melts at 125—127°.

Methodology for Testing for Action on Lipids and Lipoproteins in the Serum

Male rats of 180—200 g body weight receive the test substance, dissolved in polyethylene glycol 400, by peroral administration once daily on 3 days. On the 4th day, the animals are treated twice, in the morning and in the evening. After the last treatment, food is withheld from the animals. Sixteen hours later the rats are killed. Serum is extracted from the blood.

Equal amounts of serum from every 2 rats from the same group are combined and 0.05% EDTA (ethylenediamine-tetraacetic acid) and 0.01% thimerosal are added. The serum lipoproteins are isolated by ultracentrifugation in a Beckmann 40.3 Rotor. The VLDL (very low density lipoproteins) are obtained by centrifuging for 24 hours at 78,000 g and at the density 1.006, the LDL (low density lipoproteins) are obtained by centrifuging for 24 hours at 78,000 g and at the density 1.040, and the HDL (high density lipoproteins) are obtained by centrifuging for 24 hours at 109,000 g and at the density 1.21.

In each serum sample and in each lipoprotein fraction, the cholesterol and triglycerides are determined by enzymatic methods. LDL-cholesterol was regarded as the most important parameter for assessing lipid reduction. Literature: K. R. Müller and R. G. Cortesi, Artery 4(6): 564—577 (1978).

The figures of the following results give the changes in LDL-cholesterol as a percentage of the control. Dosage: 50 mg/kg perorally.

2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: —61%.
2-(3-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: —43%.
2-(4-methoxyphenyl)-5-propoxy-5H-[1H]benzopyrano[4,3-d]pyrimidine: —38%.
2-(5-methylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: —29%.
2-(4-hydroxyphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: —69%.

Methodology for Testing the Analgesic Action

This action is determined by evaluating the writhing syndrome in rats. The writhing syndrome is produced, for example, in female rats of 120—140 g (5 animals per group) by an intraperitoneal injection of 0.2 ml of a 3% acetic acid solution one hour after oral administration of the tested substance. The writhing movements of the test animals are counted for 20 minutes.

The analgesic (antinociceptive) activity of a compound is assessed by determining the dosage (by interpolation) that, in comparison with control animals (which have received only the carrier of the active substance), reduces the number of writhings by 50% (=ED_{50}).

Literature: Ziel *et al.*, Pain Res. and Therapy, vol. 1, ed. Bonica and Albe, Raven Press N.Y., 1976, p. 517.

The ED_{50} values are quoted in the following in mg/kg for peroral administration:

2-(4-pyridyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: 15.0 mg/kg.

2-(3-pyridyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: 1.5 mg/kg.

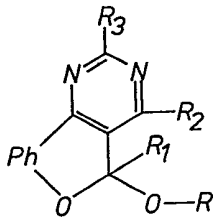
2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: 5 mg/kg.

6-methyl-2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine; 60 mg/kg.

1-(2-pyridyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine: 15 mg/kg.

Claims

1. Pharmaceutical preparations containing substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines of the general formula I



(I),

in which

Ph represents an optionally substituted 1,2-phenylene radical,

R represents a lower aliphatic hydrocarbon radical optionally substituted by a Ph_1 radical, Ph_1 being an optionally substituted phenyl radical, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a lower alkyl radical substituted by a heterocyclic radical of aromatic character, or a radical of the formula $(CH_2CH_2O)_n—CH_2CH_2OR_4$ in which *n* has the value 0, 1 or 2 and R_4 represents hydrogen or lower alkyl,

each of the symbols R_1 and R_2 represents hydrogen or lower alkyl,

R_3 represents an optionally substituted phenyl radical Ph_1, a lower alkyl radical optionally substituted by Ph_1, a cycloalkyl radical containing from 3 to 7 carbon atoms, a cycloalkyl-Ph_1 radical in which cycloalkyl and Ph_1 have the meanings given above, or a heterocyclic radical of aromatic character, and therapeutically acceptable salts of these compounds.

2. Pharmaceutical preparations according to claim 1 and containing compounds of the formula I in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, hydroxy-lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonyl-lower alkyl, halogen, halo-lower alkyl, trifluoromethyl, nitro or amino, R represents lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 7 carbon atoms, Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, or represents a lower alkyl radical substituted by a pyrryl, pyridyl or thienyl radical, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents a phenyl radical Ph_1 defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents a pyrryl, pyridyl or thienyl radical, and therapeutically acceptable salts of these compounds.

3. Pharmaceutical preparations according to claim 1 and containing compounds of the formula I in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, lower alkoxy, lower alkoxycarbonyl-lower alkyl, halogen or trifluoromethyl, R represents lower alkyl or Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents a phenyl radical Ph_1 as defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents pyridyl, and therapeutically acceptable salts of these compounds.

4. Pharmaceutical preparations according to claim 1 and containing compounds of the formula I in which Ph represents the 1,2-phenylene radical, R represents lower alkyl or phenyl-lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents lower alkyl, phenyl, lower alkoxyphenyl, phenyl-lower alkyl or pyridyl, and therapeutically acceptable salts of these compounds.

5. Pharmaceutical preparations according to claim 1 and containing compounds of the formula I in which Ph represents the 1,2-phenylene radical, R represents lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents the phenyl radical optionally substituted by lower alkoxy, and therapeutically acceptable salts of these compounds.

6. Novel substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines of the general formula I in which Ph represents an optionally substituted 1,2-phenylene radical, R represents a lower

aliphatic hydrocarbon radical optionally substituted by a Ph_1 radical, Ph_1 being an optionally substituted phenyl radical, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a lower alkyl radical substituted by a heterocyclic radical of aromatic character, or a radical of the formula $(CH_2CH_2O)_n$—$CH_2CH_2OR_4$ in which *n* has the value 0, 1 or 2 and R_4 represents hydrogen or lower alkyl, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents an optionally substituted phenyl radical Ph_1, a lower alkyl radical optionally substituted by Ph_1, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a cycloalkyl-Ph_1 radical, wherein cycloalkyl and Ph_1 have the meanings given above, or a heterocyclic radical of aromatic character, and their salts, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof.

7. Compounds of the formula I according to claim 6 in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, hydroxy-lower alkyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonyl-lower alkyl, halogen, halo-lower alkyl, trifluoromethyl, nitro or amino, R represents lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 7 carbon atoms, Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, or a lower alkyl radical substituted by a pyrryl, pyridyl or thienyl radical, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents a phenyl radical Ph_1 defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents a pyrryl, pyridyl or thienyl radical, and their salts, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof.

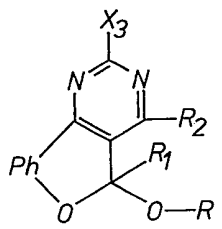
8. Compounds of the formula I according to claim 6 in which Ph represents a 1,2-phenylene radical that may optionally be substituted by hydroxy, lower alkyl, lower alkoxy, lower alkoxycarbonyl-lower alkyl, halogen or trifluoromethyl, R represents lower alkyl or Ph_1-lower alkyl, wherein the phenyl radical Ph_1 can be substituted analogously to the radical Ph mentioned above, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents a phenyl radical Ph_1 as defined above, a lower alkyl radical optionally substituted by such a phenyl radical Ph_1, or represents pyridyl, and their salts, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof.

9. Compounds of the formula I according to claim 6 in which Ph represents the 1,2-phenylene radical, R represents lower alkyl or phenyl-lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents lower alkyl, phenyl, lower alkoxy-phenyl, phenyl-lower alkyl or pyridyl, and their salts.

10. Compounds of the formula I according to claim 6 in which Ph represents the 1,2-phenylene radical, R represents lower alkyl, each of the symbols R_1 and R_2 represents hydrogen, R_3 represents the phenyl radical optionally substituted by lower alkoxy, and their salts.

11. 2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
12. 2-phenyl-5-methoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
13. 2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
14. 2-phenyl-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
15. 2-phenyl-5-isopropoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
16. 2-phenyl-5-pentyloxy-5H-[1]benzopyrano [4,3-d]pyrimidine.
17. 2-phenyl-5-hexyloxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
18. 8,9-trimethylene-2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
19. 8,9-tetramethylene-2-phenyl-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
20. 8-phenyl-11-ethoxy-11H-naphtho[1',2';7,8]pyrano[4,3-d]pyrimidine.
21. 2-(2-pyridyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
22. 2-(4-pyridyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
23. 2-(3-pyridyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
24. 2-(3-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
25. 2-(4-cyclohexylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
26. 2-(4-chlorophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
27. 2-(3-methylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
28. 2-(4-ethoxycarbonylmethylphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
29. 8,9-dimethyl-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
30. 9-ethyl-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
31. 7-methyl-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
32. 9-chloro-2-phenyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
33. 9-chloro-2-phenyl-5-isopropoxy-5H-[1] benzopyrano[4,3-d]pyrimidine.
34. 2-(4-methoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
35. 2-methyl-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
36. 2-(3,4-dimethoxybenzyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
37. 2-(3,5-dimethoxyphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.

38. 2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
39. 2-(4-hydroxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
40. 2-phenyl-5-butoxy-9-chloro-5H-[1]benzopyrano[4,3-d]pyrimidine.
41. 2-(3-methylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
42. 2-(4-methoxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
43. 2-(3-methoxyphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
44. 2-(4-ethoxycarbonylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
45. 2-(4-ethoxycarbonylmethylphenyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
46. 2-phenyl-5-methyl-5-ethoxy-[1]benzopyrano[4,3-d]-pyrimidine.
47. 2-(4-hydroxyphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
48. 2-(4-methoxycarbonylphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
49. 2-(3)-pyridyl)-5-methoxy-5H-[1]benzopyrano]4,3-d]pyrimidine.
50. 2-(3-pyridyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
51. 8-ethyl-2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
52. 6-methyl-2-(3-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
53. 2-(4-pyridyl)-5-methoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
54. 2-(4-pyridyl)-5-butoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
55. 2-(4-methoxyphenyl)-5-isopropoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
56. 2-(4-methoxyphenyl)-5-ethoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
57. 2-(4-chloromethylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
58. 2-(4-hydroxymethylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
59. 2-(4-nitrophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
60. 2-(3-trifluoromethylphenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
61. 2-(4-aminophenyl)-5-propoxy-5H-[1]benzopyrano[4,3-d]pyrimidine.
62. Salts of the compounds claimed in claims 11 to 48.
63. Salts of the compounds claimed in claims 49 to 61.
64. Therapeutically acceptable salts of the compounds claimed in claims 11 to 48.
65. Therapeutically acceptable salts of the compounds mentioned in claims 49 to 61.
66. Compounds of formula I according to claim 6 substantially as described with reference to any of Examples 1 to 25.
67. Pharmaceutical preparations containing a compound according to any one of claims 11 to 48 and 64 together with a pharmaceutical carrier.
68. Pharmaceutical preparations containing a compound according to any one of claims 49 to 61 and 65 together with a pharmaceutical carrier.
69. The compounds claimed in claims 6 to 48 and 64 for use in a method for the therapeutic treatment of the human or animal body.
70. The compounds claimed in claims 49 to 61 and 65 when used in a method for the therapeutic treatment of the human or animal body.
71. The compounds claimed in claims 6 to 48 and 64 when used as lipid-reducing agents, anti-arteriosclerotics and analgesics.
72. The compounds claimed in claims 49 to 61 and 65 when used as lipid-reducing agents, anti-arteriosclerotics and analgesics.
73. Use of compounds of claims 6 to 48 and 64 for the manufacture of pharmaceutical preparations.
74. Use of compounds of claims 49 to 61 and 65 for the manufacture of pharmaceutical preparations.
75. The novel compounds mentioned in the description.
76. Process for the manufacture of novel substituted ethers of 5-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidines of the general formula I

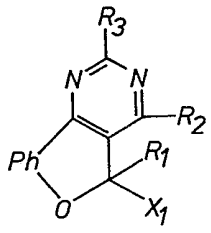


(I),

in which Ph represents an optionally substituted 1,2-phenylene radical, R represents a lower aliphatic hydrocarbon radical optionally substituted by a Ph_1 radical, Ph_1 being an optionally substituted phenyl radical, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a lower alkyl radical substituted by a heterocyclic radical of aromatic character, or a radical of the formula $(CH_2CH_2O)_n$—$CH_2CH_2OR_4$ in which *n* has the value 0, 1 or 2 and R_4 represents hydrogen or lower alkyl, each of the symbols R_1 and R_2 represents hydrogen or lower alkyl, R_3 represents an optionally substituted phenyl radical Ph_1, a

lower alkyl radical optionally substituted by Ph_1, or a cycloalkyl radical containing from 3 to 7 carbon atoms, a cycloalkyl-Ph_1 radical, wherein cycloalkyl and Ph_1 have the meanings given above, or a heterocylic radical of aromatic character, and their salts, with the exception of the compound of the formula I in which Ph represents unsubstituted 1,2-phenylene, R represents ethyl, each of the symbols R_1 and R_3 represents methyl, R_2 represents hydrogen, and the perchlorate thereof, characterised in that

a) a compound of the general formula II is etherified with a compound of the general formula III

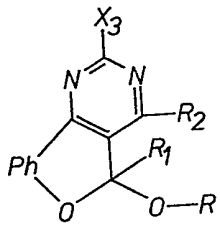


(II)

with X_2—R (III)

in which one of the radicals X_1 and X_2 represents a free, metallated or reactive esterified hydroxy group and the other respectively represents a free, reactive esterified or metallated hydroxy group, or X_2 together with the radical R in the compound X_2—R represents a compound that introduces the radical R if X_1 represents a free hydroxy group, or

b) a compound of the general formula IV



(IV),

in which X_3 represents a group that can be split off, is condensed with an organometallic compound of the formula R_3—M in which M represents a metallic grouping, or with an R_3-halide in the presence of a metal, and, if desired, a resulting compound of the formula I is converted into a different compound according to the invention, and/or, if desired, a resulting free compound is converted into a salt or a salt is converted into the free compound or into a different salt, and/or, if desired, a resulting mixture of isomers or racemates is separated into the individual isomers or racemates, and/or, if desired, resulting racemates are split into the optical antipodes.

77. A process according to claim 76 substantially as described in any of Examples 1 to 12.

78. A process according to claim 76 substantially as described in any of Examples 13 to 25.

79. The novel compounds obtainable by the process of claim 76 or 78.

80. The compounds obtainable by the process of claim 77.

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