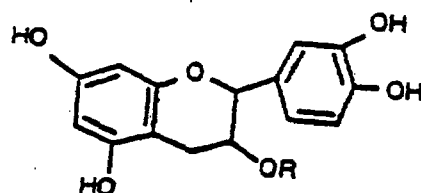


O-Substituted derivatives of (+)-cyanidan-3-ol, processes for their preparation, and pharmaceutical compositions containing these compounds and their preparation

The invention relates to new O-substituted derivatives of (+)-cyanidan-3-ol of the formula



(I)

wherein R can be an alkyl or alkenyl radical which is unsubstituted or substituted by hydroxyl, lower alkanoyloxy, lower alkyloxy, lower alkanoyl, cyano, amino, mono- or di-lower alkyl-amino, lower alkyleneamino, oxa- or aza-lower alkylene-amino, carbamoyl, mono- or di-lower alkyl-carbamoyl or halogen atoms, or can be a cycloalkyl radical which has 3 to 6 ring carbon atoms and is unsubstituted or substituted by one or more radicals from the group comprising hydroxyl-, lower alkoxy, lower alkyl, carboxyl, oxo, lower alkanoyl, amino, mono- or di-alkyl-amino or carbo-lower alkoxy, or can be a cycloalkyl-lower alkyl radical, which has 3 to 6 carbon atoms in the ring and can be unsubstituted or substituted by at least one lower alkyl radical, or can be a phenyl or naphthyl radical, which can be Mono- (sic), di- or trisubstituted by hydroxyl, lower alkoxy, carboxyl, carbo-lower alkoxy, nitro, amino- (sic), mono- or di-lower alkylamino or halogen atoms, or can be a phenyl- or naphthyl-lower alkyl or -lower alkenyl.



radical, which can be mono-, di- or trisubstituted in the aromatic nucleus by hydroxyl, lower alkoxy, carboxyl, carbo-lower alkoxy, alkanoyl, nitro, amino, mono- or dialkyl-amino, di-lower alkyl-carbamoyl or halogen atoms (excluding tri-hydroxy), or can be a saturated or unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diaza-cyclic radical, which can be fused onto a phenyl nucleus, has 2-7 carbon atoms in the heterocyclic ring and can be mono-, di- or polysubstituted by alkyl, hydroxyl, lower alkoxy, nitro, carboxyl, carbo-lower alkoxy or alkanoyloxy, or can be a heterocycl-yl-lower alkyl radical, the heterocyclic radical of which is a saturated or unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diaza-cyclic radical, or can be a radical of an alkanecarboxylic acid with at least 3 carbon atoms, lower alkenecarboxylic acid, lower alkanedicarboxylic acid or lower alkenedicarboxylic acid, or can be a cycloalkanecarboxylic acid radical which is unsubstituted or substituted by one or more radicals from the group comprising hydroxyl, lower alkyloxy, carboxyl, carbo-lower alkoxy, lower alkyl, lower alkanoyl, oxo and halogen, or can be ... (sic) benzoyl or naphthoyl radical, which can optionally be substituted by a hydroxyl, lower alkoxy, alkanoyloxy, carboxyl, carbo-lower alkoxy, nitro, amino or halogen radical, or can be a phenyl- or naphthyl-lower alkanoyl radical, which can be unsubstituted in the aromatic part or substituted by hydroxyl, lower alkoxy, carboxyl, carbo-lower alkoxy, lower alkanoyl, lower alkanoyloxy, nitro, amino, mono (sic) or di-lower alkylamino or halogen, or can be a radical of an aza-, thia-, oxa-, thiaza-, oxaza (sic) or diaza-cyclic acid, which can be saturated or unsaturated or can also be fused onto a phenyl radical, or can be an alkoxycarbonyl radical, or can be a phenyloxy-carbonyl radical, or can be a carbamoyl radical, which can optionally be mono- or disubstituted by lower alkyl radicals or phenyl or benzyl radicals, which can optionally be substituted in the ring by hydroxyl, lower alkoxy, lower alkanoyloxy or halogen atoms, or can be a radical of a lower alkyl-sulfonic acid or phenylsulfonic acid, which can be substituted

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in the ring by lower alkyl, lower alkoxy or halogen atoms, or can be the radical of a phosphoric acid which is unsubstituted or esterified by 1 or 2 lower alkyl or 1 or 2 phenyl radicals, lower denoting a radical with up to 7 C atoms, and their salts, a process for their preparation and pharmaceutical compositions containing these compounds.

An optionally substituted hydrocarbon radical R can contain 1-24 carbon atoms. An acyl radical of a carboxylic acid can contain 3-24 carbon atoms.

The radicals and compounds designated "lower" in connection with the present description preferably contain up to 4 carbon atoms.

Above and below, the general terms can have the following meaning:

An alkyl radical is preferably a lower alkyl radical, such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, butyl or sec.- or tert.-butyl, but also pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, octyl, nonyl, decyl, indecyl, dodecyl, tricosyl, tetracosyl and isomers thereof. An alkenyl radical is preferably a lower alkenyl radical, for example vinyl, allyl, n-propenyl, isopropenyl, 2- or 3-methylallyl or 3-butenyl. An alkynyl radical is, for example, the propargyl or 2-butyryl radical.

The acyl radicals of alkanecarboxylic acids are, with at least 3 carbon atoms, in particular those of propionic acid, butyric acid, isobutyric acid, valeric acid and higher homologues thereof up to stearic acid, and those of the alkanedicarboxylic acids have, for example, 2 - 10, preferably 3 - 6 carbon atoms and the lower alkenedicarboxylic acids have, for example, 4 - 7 carbon atoms. Of these, there should be mentioned: 2-methyl-succinic acid, glutaric acid, 3-methyl-glutaric acid, 3-ethylglutaric acid, adipic acids (sic), pimelic acid, suberanic (sic) acid, azealic (sic) acid or sebacic acid, preferably malonic acid and succinic acid. Acyl radicals of unsaturated aliphatic acids which may be mentioned in particular are those of acrylic acids and propionyl (sic), methacrylic, crotonic or oleic acid, and



above all of maleic acid or fumaric acid.

The acyl radicals of carbocyclic acids are above all those of cyclohexane-carboxylic acid and benzoic acids, which can be substituted, for example, by lower alkyl, such as methyl, alkoxyl, such as methoxy or ethoxy, or a carboxyl group; of these, phthalic acid, isophthalic acid, terephthalic acid, cinnamic acid or toluene (sic) acid, and also 1- or 2-naphthoic acid or 1,2-cyclohexanedicarboxylic acid may be mentioned in particular.

The acyl radicals of heterocyclic acids are, for example, those of pyranicarboxylic acid, thienylcarboxylic acid and nicotinic, isonicotinic or picolinic acid.

A lower alkoxycarbonyl group is, in particular, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert.-butoxycarbonyl or tert.-pentoxycarbonyl.

Optionally N-substituted carbamoyl groups are, for example, N-lower alkyl (sic) or N,N-di-lower alkyl-carbamoyl, such as N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, and N-aryl-, N,N-diaryl- or N-aryl-N-alkyl-carbamoyl, such as N-phenyl-, N,N-diphenyl- or N-phenyl-N-methyl- or -ethyl-carbamoyl, which can be unsubstituted or substituted in the phenyl nucleus.

A lower alkoxy group is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.- or tert.-butoxy, n-pentoxy or tert.-pentoxy.

A halogen is, for example, bromine, iodine or, in particular, chlorine or fluorine.

A mono- or di-lower alkyl group is, for example, methylamino, dimethylamino, ethylamino or diethylamino.

A lower alkyleneamino group, which can also be interrupted by hetero atoms, is, for example, pyrrolidino, piperidino (sic), morpholino, thiamorpholino or 4-methyl-piperazino.

The new compounds which contain a salt-forming radical can also exist in the form of their salts.

Salts which should be mentioned of compounds with a free carboxylic acid are, for example, metal salts, in particular those with alkali metals, such as sodium or potassium,



or with alkaline earth metals, such as magnesium or calcium, or, for example, with zinc, copper, iron, silver or mercury, or with ammonium, for example ammonia or organic bases, such as lower alkylamines, for example trimethylamines (sic) or triethylamine, and especially non-toxic and pharmaceutically usable salts of the above type.

The new compounds which contain basic groups can form acid addition salts, in particular with non-toxic pharmaceutically usable acids, such as mineral acids, for example hydrochloric acid or hydrobromic acid, sulfuric acids, phosphoric acid, carboxylic acids or organic sulfonic acids, for example aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aromatic, araliphatic, heterocyclic or heterocyclic-aliphatic acids, for example acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, maleic acid, citric acid, tartaric acid, ascorbic acid, maleic acid (sic), phenylacetic acid, benzylic (sic) acid, 4-aminobenzylic (sic) acid, anthranilic acid, 4-hydroxybenzoic acid, salicylic acid, aminosalicilic acid, embonic acid or nicotinic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, phenylsulfonic acid, 4-methyl-phenylsulfonic acid, naphthalenesulfonic acid, sulfanilic acid or cyclohexylsulfanylic (sic) acid.

The new compounds which contain basic groups can also be present in the form of their quaternary ammonium compounds.

The new compounds have useful pharmacological properties. In particular, they have an interesting activity in preventing hepatic necrosis and they prevent lipoperoxidation. They can also prevent collagen degradation, and furthermore the activity of the lysosomal (sic) enzymes by increasing the stability of the lysosomal membranes. They can also influence permeability and vascular tone.

The new compounds are particularly suitable for the treatment of liver diseases, such as acute hepatitis (viral, alcoholic or toxic), steatosis and chronic hepatitis, in particular as a consequence of alcohol abuse. They can also be used for the treatment of diseases which ... (sic) a

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change in conjunctival tissue, in particular congenital diseases of collagen, such as Ehlers-Danlos disease, Marfan syndrome and cutis laxa, as well as scoliosis, osteoporosis, scleroderma and periodontosis, for healing wounds, especially in cases of decubitus ulcers, and also on certain forms of rheumatism, especially osteoarthritis. They can also be used for circulatory disturbances of a venous or arterial nature.

Thus, for example, the activity can ... (sic) on the normal or pathological metabolism of hepatocytes of rats which have been isolated by the technique of Berry and Friend [J. Cell. Biol. 43, 506-520 (1969)] and have been incubated in 2 ml of a physiological Krebs-Ringer solution in the presence of 0.5 to 5 mg of the new products and to which various hepatotoxic substances are added, or by the prevention of lipoperoxidation by carbon tetrachloride in accordance with the method of Comporti, Sacconi and Danzani [Enzymologia 28, 185-203 (1965)], the intensity of the lipoperoxidation in the presence of 5 to 50 μ g per 4 ml being evaluated by the amount of malonodialdehyde formed. The change in experimental hepatitis induced by galactosamines, carbon tetrachloride or ethanol can be demonstrated on rats which have received the new products orally or intraperitoneally in doses of 100 - 500 mg/kg. In the acute stages, the animals are sacrificed 24 or 4 hours after administration of the toxic agent and the condition of the liver is evaluated with the following tests: clearance in BSP, the amount of bilirubin in the plasma, the amount of transaminase in the plasma, the amount of triglycerin and lipids in the liver and in the serum and the serum lipoproteins. It is thus demonstrated that the new substances are capable of favourably influencing the liver regeneration process and of triggering off an immunostimulating effect.

The effectiveness of the new compound (sic) in protecting the conjunctival tissue can be demonstrated by the prevention of collagen degradation by collagenase with 0.1 to 5 mg/2 ml of the new substances or by the prevention of the activity of the lysosomal (sic) enzymes and the increase in

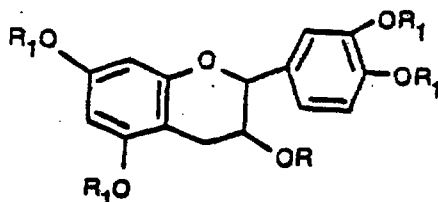
the stability of the lysosomal membranes by means of 0.05 to 0.2 mg/1 ml of the new compound (sic) in accordance with the method of P. Niebes and Ponard [biochem. Pharmacol. 24, 905 (1975)], or also by the experimental lathyrism in rats, to which 100 mg/kg/day of aminoacetonitrile are given perorally or 250 mg/kg/day of iminodipropionitrile are given subcutaneously for 7 days or 600 mg/kg/day of β -aminopropionitrile are given orally for 3 weeks, and to which 100 - 500 mg/kg of the new products are given orally for 3 weeks before, during or after the poisoning. At doses of 100 - 500 mg/kg given parenterally or orally to these animals, these new substances can a) reduce the experimental oedema caused by galactosamine and dextran, b) reduce the capillary permeability in rats measured by diffusion of trypan blue [V.L. Beach and B.G. Steinetz, J. pharmacol. Exp. Ther. 131, 400 (1961)], c) reduce the retro-auricular venal flow in the rabbit ear and d) promote cleansing of ischaemic paws of dogs from tissue lactic acid.

It was hitherto not possible to observe the activity of these new compounds with these indications. Until now, it was known that (+)-cyanidan-3-ol has a protective effect on the liver. It is surprising that the new compounds have additional and higher activities than those of (+)-cyanidan-3-ol.

The invention particularly relates to the compounds of the formula I described in the examples.

The parent substance, (+)-cyanidan-3-ol, and some derivatives were ... (sic) from the literature (see Liebig's Ann. (sic) Chem. 714, 193 - 204 (1968); German Patent A-2,711,927; German Patent A-2,206,570; Belgian Patent A-742,074; German Patent A-2,740,346 and German Patent A-2,109,602). A comparison of the action of compounds obtainable according to the invention (3-O-butyryl-(+)-cyanidan-3-ol (sic)) with a compound according to the prior art (penta-O-butyryl-3,5,7,3',4'-(+)-cyanidan-3-ol, according to German Patent A-2,711,927) showed a surprising superiority of the compound obtainable according to the invention in hepatitis induced by galactosamine in the rat (sic) (as described above).

The new compounds can be obtained in a manner which is known per se. Thus, for example, they can be obtained by a process in which, in a compound of the formula II



(II)

wherein R_1O represents a protected hydroxyl group which can easily be hydrolysed or hydrogenolysed and R has the above-mentioned meaning, the radical OR_1 is split to give the hydroxyl group and, if desired, a radical R in a resulting compound is converted by reduction, and/or in that (sic) a resulting salt is converted into the free compound or a free compound with salt-forming groups is converted into a salt.

In the compounds of the formula II, the radical R_1 can ... (sic) a lower alkyl radical, which is mono-, die- (sic) or polysubstituted, a lower alkenyl radical, an unsubstituted or mono-, di- or trisubstituted araliphatic radical, an aliphatic, aromatic or araliphatic carboxylic acid radical or an esterified carbonic acid radical, or a radical which forms a cyclic acetal with the oxygen atom bonded to R_1 .

If R_1 represents a lower alkyl radical, this preferably contains 1 - 4 carbon atoms and is above all methyl or ethyl. These radicals can be substituted by lower alkoxy, for example ethoxy or methoxy, or lower alkoxy-ethoxy, for example methoxyethoxy.

If R_1 is a lower alkylenyl radical, this preferably contains 2 - 5 carbon atoms and is above all allyl, methallyl, 2-butenyl or 2-pentenyl.

If R_1 is an araliphatic radical, in particular a benzyl radical, this can be substituted by various substituents, for example by one or more alkyl radicals with 1 - 4 carbon atoms, such as methyl, ethyl, isopropyl or tert.-propyl, by one or more halogens, preferably chlorine, bromine or fluorine, one or more alkoxy radicals, such as methoxy or

ethoxy, or by nitrile. These substituents can occupy the ortho- and para-position; they are preferably in the para-position. If a substituent in the radical R_1 is a substituent of the second order, such as the nitro group, it is preferably in the meta-position.

If the radical R_1 is an aliphatic acyl radical, the aliphatic part is, for example, alkyl with 1 - 4 carbon atoms, and preferably methyl or ethyl, which can be substituted by lower alkoxy, such as methoxy. If R_1 is an aromatic or araliphatic acyl radical, the aromatic radical is, in particular, a phenyl radical, which is optionally substituted, and the aliphatic radical is an alkyl radical with 1 - 2 carbon atoms.

If R_1 is an alkoxy-carbonyl radical, the alkyl radical can in turn be substituted by an aryl radical or by a halogen atom. If R_1 , together with the oxygen which the radical R_1 carries, is an acetal, this acetal can be linear or cyclic, for example a pyranyl radical.

Radicals of the formula R_1 which should be mentioned in particular are, for example, allyl, methallyl, ethylallyl, 2-butenyl, 2-pentenyl, methoxymethyl, ethoxymethyl, methoxyethoxymethyl, acetonyl, propionylmethyl, cinnamyl, phenacyl, benzyl, 2-methylbenzyl, 4-methylbenzyl, 4-t-butyl-benzyl, 4-bromobenzyl, 4-fluorobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-ethoxybenzyl, 3-nitrobenzyl, 3,5-dinitrobenzyl, 4-cyanobenzyl, chloro-, bromo- or phenyl-phenacyl or methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl or phenoxy-carbonyl.

The OR_1 groups can be split by hydrolysis or by hydrogenolysis (sic).

The hydrolysis of these substances can be carried out with acids, but there is the risk here of the flavone structure changing and the yield correspondingly falling. p-Toluenesulfonic acid is preferably used, the reaction preferably being carried out in an alcohol, such as methanol. The reaction can take one or several dozen hours, depending on the nature of the substituents. It can be carried out at

room temperature or can also be accelerated by boiling under reflux, in which case the risk of partial decomposition of the end products must be accepted.

The group OR_1 can also be carried out (sic) by catalytic hydrogenation with molecular hydrogen or by hydrogen transfer in situ by means of a hydrogen donor, such as cyclohexene. If the compound to be hydrogenated has a salt-forming radical in the substituent R_1 , the free form or a salt thereof can be used.

The reaction is carried out in the presence of a solvent, such as water, methanol, ethanol, isopropanol, tert.-butyl alcohol, ethyl acetate, dioxane or tetrahydrofuran. It proceeds at room temperature under normal pressure, but it can also be carried out at elevated temperature and/or under increased pressure. The reaction conditions and catalysts chosen are preferably such that destruction of the flavanyl radical is avoided and, on the other hand, neither the aromatic nucleus nor the desired substituents R is destroyed. Catalysts which may be mentioned in particular are finely divided palladium or palladium-on-animal charcoal. The reaction is thereby preferably carried out at room temperature under normal pressure.

If the radicals R contain groups which can be hydrogenated, these can be simultaneously hydrogenated, particularly if highly reactive catalysts, such as palladium-on-charcoal, are used. It is also possible to leave the group R intact by reducing the activity of the catalyst.

The compounds which contain a salt-forming group, such as, for example, carboxyl groups, can be obtained in the free form or in the form of their salts, depending on the conditions used. These forms can be mutually converted into one another. Salts of compounds which contain a free carboxylic acid are, for example, metal salts, in particular alkali metal salts, for example sodium or potassium salts, and also alkaline earth metal salts, for example magnesium salts or calcium salts, or ammonium salts, for example with ammonia or organic bases, such as a tri-lower alkylamine, for

example trimethylamine or triethylamine. These salts are obtained, for example, by reacting the free compound with hydroxides or carbonates of these metals or with ammonia or amines, or with suitable ion exchangers, or with organo-metallic compounds.

Compounds which contain basic groups can also ... (sic) in the form of their acid addition salts, in particular with non-toxic pharmaceutically usable acids, for example with mineral acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid, or with organic carboxylic or sulfonic acids, for example aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aromatic, araliphatic, heterocyclic or heterocyclic-aliphatic acids, for example acetic acid, propionic acid, succinic acid, glyconic (sic) acid, lactic acid, maleic acid, tartaric acid, citric acid, ascorbic acid, phenylacetic acid, benzoic acid, 4-aminobenzoic acid, anthranilic acid, 4-hydroxybenzoic acid, salicylic acid, amino-salicylic acid, embonic acid or nicotinic acid, and also methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethylenesulfonic acid, phenylsulfonic acid, p-methylphenylsulfonic acid, naphthalenesulfonic acid, sulfanylic (sic) acid or cyclohexylsulfamic acid. These salts can be treated (sic), for example, by treatment of the free compounds containing a basic group with the acids mentioned or corresponding anion exchangers.

The new compounds containing basic groups can also be obtained as their quaternary ammonium salts, for example by treatment with alkylating agents, such as lower alkyl halides, for example methyl iodide, or lower alkyl or benzyl sulfates, such as methyl sulfate.

The starting substances for this process are known in some cases, but most of them are new. They can be obtained by a method which is known per se or, in particular, in a new and advantageous manner. Thus, for example, (+)-cyanidan-3-yl (sic) or one of its salts can be reacted with a reactive ester of an alcohol of the formula



wherein R_1 has the abovementioned meaning, and the radicals R can be introduced into the hydroxyl group in the 3-position by etherification or esterification.

A reactive ester is, in particular, an ester with a strong inorganic acid, above all with a hydrogen halide acid, such as hydrogen chloride or hydrogen bromide, or an organic sulfonic acid, preferably a lower alkanesulfonic acid, for example methane- or ethanesulfonic acid, or a benzenesulfonic acid, which can be substituted in the benzene nucleus, for example by methyl, chlorine or bromine, such as p-toluenesulfonic acid or p-bromobenzenesulfonic acid.

This process gives derivatives of (+)-cyanidan-3-ol, the 4-phenolic hydroxyl groups of which are substituted. Of these tetra-ethers, 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol has already been prepared by a pure laboratory process [K. Weinges and D. Seiler, Liebigs Ann. Chem. 714 193 - 204 (1968)]. In this process, (+)-cyanidan-3-ol, dissolved in acetone, was reacted with benzyl chloride in the presence of potassium iodide and potassium carbonate by boiling under reflux for several hours under nitrogen. This is classical benzylation and, after separation and crystallization from ethanol, it leads to a mixture of 8-benzyl-5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol. The latter is isolated in a yield of 1 - 2% by chromatography. The yield is so small that this method cannot be used industrially to prepare the tetra-substituted compounds.

If, however, the benzyl chloride is replaced by another halide selected from the radicals R_1 , the reaction can readily be carried out, especially if chlorides or bromides of unsubstituted or substituted phenacyl, for example phenacyl chloride or bromide or 4-bromophenacyl or 4-phenylphenacyl chloride or bromide is used. After the insoluble potassium carbonate has been filtered off and the acetone has been evaporated, it is sufficient to crystallize the residue in a suitable solvent, for example a mixture of acetone and methanol. The tetra-ethers are thus obtained in a good yield.

It has furthermore been found that the intermediate products can be obtained in a very good yield if (+)-cyanidan-3-ol is treated with an alkali metal hydride or alkali metal carbonate in an aprotic and organic solvent with a high dielectric constant and the resulting tetra-alkali metal salt is reacted with a reactive ester of the formula



the ratio of cyanidan-3-ol, alkali metal hydride and reactive ester being 1 : approximately 4.25 : approximately 4.5 or the ratio of cyanidan-3-ol, alkali metal carbonate and reactive ester being 1 : approximately 8 : approximately 6.

The alkali metal hydride is, in particular, sodium hydride and is preferably used in the form of a dispersion in oil. The alkali metal carbonate is, in particular, potassium carbonate.

The aprotic solvents used are, in particular, amides, such as dimethylformamide, but also sulfoxides, such as dimethyl sulfoxides. Dimethylformamide is preferred, however, for economic reasons, because it can be recovered by simple distillation under normal pressure and because it is easier to handle than dimethyl sulfoxide.

It is moreover important that the reaction medium is as dry as possible. The dimethylformamide is thus dried over a molecular sieve, and the solution of cyanidanol in dimethylformamide is dried in the same manner. The formation of by-products is thereby avoided, without the drying opposing the formation of the desired products.

The reaction can be carried out in the presence of a quaternary ammonium salt, such as tetra-n-butyl-ammonium bisulfate, which are (sic) used in a proportion of 0.1 to 0.5 mol per mol of cyanidan-ol, or a crown ether, preferably 18-crown-6, which is used in an amount of 0.5 mol per mol of cyanidan-ol.

The reaction is carried out at a temperature between -25°C and approximately $+50^{\circ}\text{C}$. Since it is known that dimethylformamide already starts to decompose at room temperature in contact with basic substances, this reaction is

preferably carried out at -25°C to $+25^{\circ}\text{C}$, and above all at approximately -5°C to approximately 0°C . With dimethyl sulfoxide, since this scarcely decomposes, the reaction can be carried out at a temperature below 50°C , preferably between $+15^{\circ}\text{C}$ and approximately $+30^{\circ}\text{C}$, for example at room temperature.

Since the alkali metal salt of (+)-cyanidan-3-ol is unstable in dimethylformamide-sodium hydride even at a low temperature, the esterifying or etherifying agent must be added immediately. If this is not done, the yield of the reaction is reduced and the phase for cleaning the desired product is made difficult. After addition of the esterifying or etherifying agent at low temperature, this temperature is further maintained for a certain period before it is slowly allowed to increase, for example to room temperature. The reaction has then ended and the reaction mixture can be kept in this state for more than 15 hours without the quality of the desired product changing. Good stirring is necessary during the reaction.

The progress of the reaction can be monitored by thin layer chromatography on silica gel using chloroform or methylene chloride as the mobile phase.

After the solvent has been removed from the reaction medium by distillation, the residue is taken up in an aprotic solvent, such as is used for crystallization of the intermediate product. Trichloroethylene is a particularly suitable solvent for crystallization of the desired product. Other solvents, such as carbon tetrachloride, toluene, ethyl acetate, ethanol, isopropanol or mixtures of these solvents, for example with carbon tetrachloride, n-hexane or acetone-methanol, also give good results. Ethylene (sic) ether and n-hexane as well as acetone, pyridine, chloroform, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran and methylene chloride, are less suitable since the new substances are soluble in these at room temperature.

The radical R is introduced into the intermediate products by methods which are known per se. Thus, for



example, a halogen derivative of the formula



can be allowed to act on these compounds, preferably in the presence of a base, such as an alkali, for example sodium hydroxide or potassium hydroxide, silver oxide, sodium amide, sodium hydride or potassium hydride. This etherification can be carried out in a non-reactive solvent, such as dioxane, tetrahydrofuran or toluene, and if appropriate also in a mixture of these solvents or a mixture with water. It is carried out at room temperature and can be accelerated by warming. The duration of the reaction is between a few minutes and several days, but in general a few hours are sufficient. If the base used is sodium carbonate or potassium carbonate in aqueous solution and the intermediate product is in a solution which is not miscible with water, use can be made of a phase transfer catalyst, such as tetra-butyl-ammonium bisulfate.

If R is a hydroxyalkyl radical or an aminoalkyl radical, the derivatives of the formula II can also be obtained by condensation with epoxide or with aziridine in a basic or acid medium.

If R is an aromatic radical, the derivatives of the formula II can be obtained by reaction with an aromatic halide. This reaction is carried out in an inert solvent, such as tetrahydrofuran, at room temperature or elevated temperature in the presence of a base, such as a tertiary amine, for example trimethylamine or triethylamine, or a fluoride, such as potassium fluoride, or a quaternary ammonium salt in the presence, for example, of a crown ether. An alcoholate of the intermediate products reacts, for example, with a heterocyclic halide, and it is also possible to use an aromatic diester of phosphoric acid in the presence of a catalytic amount of a sulfonic acid, such as p-toluene-sulfonic acid. The intermediate products of the formula II in which R is hydrogen add on olefines which are substituted

by electron-withdrawing groups, such as nitrile, nitro, ketones or esters, in the presence of a base. The participants in the reaction can be dissolved in an inert water-immiscible solvent and the base can then be 50% strength aqueous sodium carbonate. It is also possible to use a phase transfer catalyst, such as benzyltrimethylammonium hydroxide. A derivative of an acid of the formula



such as an acid halide, an anhydride or a cyanide, which can also be formed in situ, is preferably used to introduce the radical R into the intermediate products. A basic solvent, such as pyridine, in the absence or presence of a tertiary aliphatic amine, such as triethylamine and/or pyridine, or a mixture of solvents, at least one of which is basic, or an inert solvent or a basic solvent and a catalyst, preferably an alkali, is used. This reaction also proceeds with N-substituted isocyanates.

The esters of a mineral acid or of a sulfonic acid with the intermediate products can ... (sic) by reaction of these with a halide of the acids mentioned or with a mineral polyacid which is still suitable for esterification and in which one or two hydroxyl groups are substituted or blocked. The protective groups are then split off, individually or together with the radicals R_1 , by hydrolysis or by hydrogenolysis. The esters with mineral acids can also be obtained by reaction of their anhydrides. As a consequence of the close relationships between the new compounds in the free form and in the form of their salts, where appropriate the free compounds above and below are accordingly and suitably also to be understood as the corresponding salts. The substituents R can be chiral and the new compounds can be present as pure stereoisomers or stereoisomeric mixtures. The latter can be resolved into the pure stereoisomers on the basis of their physicochemical properties in a manner which is known per se, for example with the aid of chromatographic

separation, such as thin layer chromatography, or any other suitable separating agent. The more active of the stereoisomers is preferably isolated.

The processes described above are carried out in a manner which is known per se, in the presence or absence of solvents and diluents, and if necessary with cooling or warming, under increased pressure and/or under an inert gas atmosphere, such as nitrogen. The invention also relates to those embodiments of the process in which a compound obtainable as an intermediate product at any stage of the process is used as the starting substance and the missing process steps are carried out, or in which a starting substance is formed under the reaction conditions, or in which a reaction component is used, where appropriate, in the form of its derivatives, such as its salts, and/or in the form of isomer mixtures or pure isomers.

The present invention likewise relates to pharmaceutical products which contain compounds of the formula I or pharmaceutically usable salts of such compounds with salt-forming groups. They contain an effective amount of the active substances together or as mixtures with organic or mineral excipient substances, which can be solid or liquid and which are suitable for enteral or parenteral administration. Tablets or gelatine capsules containing the active substances together with a diluent, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and/or lubricants, such as silicon (sic), talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol, are preferably used; the tablets also contain binders, for example magnesium or aluminium silicate, starches, such as maize, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose, carboxymethylcellulose and/or polyvinylpyrrolidone, and if desired also disintegrating agents, such as starch, alginic acid or salts thereof, such as sodium alginate, or absorbents, dyestuffs, substances which improve the taste and/or sweeteners. The injection products are, for example, solutions or suspensions

in isotonic water, and the suppositories are, above all, fat emulsions or suspensions. The pharmaceutical products can be sterilized and/or contain auxiliaries, such as preservatives and stabilizing agents and/or emulsifying agents, salts which regulate the osmotic pressure and/or stabilizers. The pharmaceutical products mentioned are obtained in a manner which is known per se, for example with the aid of granulation and tablet coating, and contain between 0.1 to 75% and in particular between 1 and 50% of the active compounds.

The substances according to the invention are administered in a dose of 1 to 100 mg, preferably 1 to 500 mg per dose unit.

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

Example 1

A suspension of 12 g of palladium chloride PdCl_2 in 1,800 ml of methanol is hydrogenated at room temperature in a 3 litre flask for 2 hours, 2,400 ml of hydrogen being consumed. The methanol is decanted off and the palladium black formed is washed 4 times with 800 ml of methanol, the hydrogen chloride formed and traces of palladium chloride being removed. The product is then washed 3 times with 500 ml of ethyl acetate. During the last decanting process, a thin layer of ethyl acetate is left over the palladium black to prevent spontaneous ignition.

40 g of 5,7,3',4'-tetra-O-benzyl-3-O-methyl-(+)-cyanidan-3-ol in 1,600 ml of ethyl acetate are added to this suspension and hydrogenation is carried out for 3 hours, about 6,600 ml of hydrogen being consumed. The mixture is filtered and the filtrate is evaporated in vacuo at 40° . The residue is taken up in 2,000 ml of water and the mixture is concentrated in vacuo at 40° to a volume of about 100 ml. This purification is repeated 3 times and, finally, the product is dried by lyophilization. 18.5 g of 3-O-methyl-(+)-cyanidan-3-ol of melting point = $118 - 120$ and $(\alpha)_D^{29} = +2.76$ (ethanol, $c = 0.5$) are thus obtained.

Example 2

6.0 g of palladium chloride are hydrogenated in 900 ml of methanol in a 2 litre flask at room temperature for 1 1/2 hours, approximately 1,100 ml of hydrogen being consumed. The methanol is decanted and the product is washed 3 times with 200 ml of methanol and then 3 times with 200 ml of ethyl acetate.

A solution of 21.2 g of 5,7,3',4'-tetra-O-benzyl-3-O-butyl-(+)-cyanidan-3-ol in 900 ml of ethyl acetate is added and hydrogenation is carried out at room temperature for 5 hours; about 3,250 ml of hydrogen are consumed. The palladium is filtered off and the filtrate is evaporated in vacuo at 40°C. The residue is taken up in 500 ml of water and the mixture is evaporated to a volume of approximately 50 ml. This procedure is repeated 4 times. After the last evaporation, the product is dried to constant weight under 10 mm Hg at 60°. 3-O-Butyl-(+)-cyanidan-3-ol of melting point 103 - 104° is thus obtained.

Example 3

The procedure followed is as described in Example 2, but 21.6 g of 5,7,3',4'-tetra-O-benzyl-3-O-butyryl-(+)-cyanidan-3-ol are used as the starting substance. After drying, the product is dissolved in a mixture of 5,500 ml of water and 1,100 ml of ethanol at room temperature, the solution is filtered and the filtrate is evaporated to dryness in vacuo at 40°. The solution is decanted and is left to stand at 4° for 3 days. The white precipitate which forms is filtered off, washed with cold water and dried to constant weight under 10 mm Hg over phosphorus pentoxide at 50°C. 3-O-Butyryl-(+)-cyanidan-3-ol of melting point 112 - 113°C is thus obtained.

Example 4

The procedure followed is as in Example 2, to give 3-O-(3,3-dimethyl-butanoyl)-(+)-cyanidan-3-ol of melting point 118 - 120°C from 22 g of 5,3',4'-tetra-O-benzyl-3-O-(3,3-dimethyl-butanoyl)-(+)-cyanidan-3-ol.

Example 5

The procedure followed is as in Example 2, but 22 g

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of 5,7,3',4'-tetra-0-benzyl-3-(3-carboxypropionyl)-(+)-cyanidan-3-ol are used as the starting substance. After removal of the ethyl acetate and toluene by azeotrope formation with water, the residue is dissolved in 1,000 ml of water, the solution is evaporated until a slight cloudiness appears (about 500 ml) and is filtered and the filtrate is lyophilized to constant weight. 3-O-(3-Carboxy-propionyl)-(+)-cyanidan-3-ol of melting point 102 - 106°C is thus obtained.

Example 6

The procedure followed is as in Example 1, but 50 g of 5,7,3',4'-tetra-0-benzyl-3-O-decanoyl-(+)-cyanidan-3-ol are used as the starting substance. After evaporation of the ethyl acetate, the residue is dried in vacuo at 40°C and dissolved in 300 ml of ethanol, the solution is concentrated to 50 ml, 250 ml of ethanol and 250 ml of water are added and the solvent is evaporated off in vacuo at 40°C. The residue is dried to constant weight under a high vacuum over phosphorus pentoxide. 3-O-Decanoyl-(+)-cyanidan-3-ol of melting point 71 - 74°C is thus obtained.

Example 7

A solution of 26.6 g of 5,7,3',4'-tetra-0-benzyl-3-O-palmitoyl-(+)-cyanidan-3-ol in 900 ml of ethyl acetate (solution is achieved by gentle warming) is introduced into a two litre flask. 16.0 g of palladium-on-charcoal (10% strength) are then added and the mixture is hydrogenated. The palladium is separated off by filtration and the filtrate is evaporated to dryness. The residue, a glutinous mass, is taken up in 400 ml of hot methanol. 1,500 ml of water are added, with stirring, and stirring is continued at room temperature for one night and then in an ice-bath for 48 hours. The precipitate formed is filtered off and dried under a high vacuum over phosphorus pentoxide at room temperature. The resulting 3-O-palmitoyl-(+)-cyanidan-3-ol has a melting point of 67 - 69°C.

Example 8

The procedure followed is as described in Example 2: the palladium black is obtained by hydrogenation of 18 g of

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palladium chloride in 900 ml of ethyl acetate, and 40 g of 5,7,3',4'-tetra-benzyl-3-O-tetrahydrophthalyl-(+)-cyanidan-3-ol in 1,800 ml of ethyl acetate are then hydrogenated as in Example 1. After removal of the organic solvents by forming an azeotrope with water, the residue is dried to constant weight under a high vacuum over phosphorus pentoxide. 3-O-(2-Carboxy-cyclohexane-carbonyl)-(+)-cyanidan-3-ol of melting point 138 - 140°C is thus obtained.

Example 9

30 g of palladium chloride which have been suspended in 4.5 l of methanol are hydrogenated in a 10 l flask. The reaction takes one hour and consumes approximately 4.92 l of hydrogen. The resulting palladium black is washed 4 times with in each case one litre of methanol and then 4 times with in each case one litre of ethyl acetate. A solution of 113 g of 5,7,3',4'-O-tetra-benzyl-2-O-benzoyl-(+)-cyanidan-3-ol in 4 litres of ethyl acetate are added to the catalyst, mixed with a little ethyl acetate. The mixture is hydrogenated for approximately 1 1/2 hours, the catalyst is filtered off and washed with 250 ml of ethyl acetate and the filtrates are combined and distilled under reduced pressure at 40°C. The residue is taken up in 5 litres of water and the resulting suspension is stirred at room temperature for 30 minutes and then evaporated in vacuo at 40°C to a volume of approximately 500 ml. This is repeated twice and, finally, the product is dried to constant weight over silica gel under a high vacuum. Amorphous 3-O-benzoyl-(+)-cyanidan-3-ol of melting point 132 - 135°C is thus obtained.

Example 10

3-O-(4-Fluoro-benzoyl)-(+)-cyanidan-3-ol of melting point 131 - 133°C is obtained analogously to Example 9, but using 115.8 g of 5,7,3',4'-tetra-O-(4-fluoro-benzoyl)-(+)-cyanidan-3-ol as the starting substance.

Example 11

As in Example 9, the palladium black is prepared starting from 40 g of palladium chloride suspended in 4.5 litres of methanol, the methanol is replaced by ethyl acetate

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and 130 g of 5,7,3',4'-tetra-0-benzyl-3-0-(3,4-dibenzoyloxy-benzoyl)-(+) -cyanidan-3-ol, dissolved in 5.5 l of ethyl acetate, are hydrogenated. The organic solvents are removed by forming an azeotrope with water, the residue is dissolved in 500 ml of water and the product is lyophilized to constant weight. 3-0-Protocatechyl-(+) -cyanidan-3-ol of melting point 166 - 168°C is thus obtained.

Example 12

The procedure followed is as described in Example 2, to give 3-0-acetylsalicylyl-(+) -cyanidan-3-ol of melting point 118 - 119°C from 24.5 g of 5,7,3',4'-0-tetra-benzyl-3-0-acetylsalicylyl-(+) -cyanidan-3-ol.

Example 13

Analogously to Example 1, palladium black is prepared from 24 g of palladium chloride in 3.6 l of methanol and 64 g of 5,7,3'-4'-0-tetra-benzyl-3-(2-carboxy-benzoyl)-(+) -cyanidan-3-ol in 3.5 l of ethyl acetate are hydrogenated. After the catalyst has been filtered off and the organic solvents have been evaporated off, the residue is taken up in 2 litres of ethanol, the solution is concentrated to about 100 ml, this procedure is repeated twice and the residue is then dried to constant weight at 40°C under a high vacuum. 3-0-(2-Carboxy-benzoyl)-(+) -cyanidan-3-ol of melting point 139 - 142°C is thus obtained.

Example 14

Palladium black is prepared as described in Example 1, the methanol is then replaced by ethyl acetate and 30.8 g of 5,7,3',4'-tetra-0-benzyl-3-(N-phenylcarbamoyl)-(+) -cyanidan-3-ol in 1,600 ml of ethyl acetate are hydrogenated. After the catalyst has been filtered off, the filtrate is evaporated to a volume of approximately 50 ml, 250 ml of water are added and the pH is brought to 6 with aqueous sodium hydroxide solution (1N). The mixture is evaporated in vacuo at 40°C, 500 ml of water are then added and the mixture is evaporated again. This procedure is repeated 3 times, the residue is dissolved in 1 litre of ethanol and the solution is evaporated again. This procedure is repeated,

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the product is then taken up in a mixture of 300 ml of ethanol and 300 ml of water, the mixture is evaporated and, finally, the residue is taken up in 500 ml of water. The mixture is evaporated to a volume of approximately 100 ml and the precipitate formed is filtered off and dried to constant weight in vacuo. 3-O-(N-Phenylcarbamoyl)-(+)-cyanidan-4-ol of melting point 189 - 200°C is thus obtained.

Example 15

The procedure followed is as described in Example 2, but 18.2 g of 5,7,3',4'-tetra-O-benzyl-3-O-methanesulfonyl-(+)-cyanidan-3-ol are used as the starting substance and are hydrogenated in 600 ml of ethyl acetate. The solvent is distilled off at room temperature and the residue is dried at room temperature under a high vacuum. The residue is taken up in 500 ml of ethanol at room temperature, the mixture is then concentrated under a high vacuum at 0°C to approximately 50 ml, this procedure is repeated twice and the product is then dried at 35°C in vacuo in the course of 15 minutes and brought to constant weight under a high vacuum at room temperature. 3-O-Methanesulfonyl-(+)-cyanidan-3-ol is thus obtained. This substance already decomposes slowly at room temperature; it can be kept in a refrigerator at -30°C for several days.

Example 16

As described in Example 7, a solution of 40 g of 5,7,3',4'-tetra-O-benzyl-3-O-(4-methyl-benzenesulfonyl)-(+)-cyanidan-3-ol in 1.8 l of ethyl acetate is hydrogenated with 20 g of palladium-on-charcoal (10% strength) in a 3 litre flask. The hydrogenation takes 2 1/2 hours. The palladium and the charcoal are filtered off, the filtrate is evaporated to dryness in vacuo at room temperature, 1.7 l of ethanol are added and the mixture is distilled at 0°C under a high vacuum. When the volume has reached approximately 100 ml, 800 ml of ethanol are added and distillation is continued at 0°C. The residue is warmed to 35°C under a high vacuum in the course of 15 minutes and is kept at this temperature until it reaches constant weight. 3-O-(4-Methyl-benzenesulfonyl)-(+)-

cyanidan-3-ol is thus obtained. To prevent decomposition, it is kept in a refrigerator at -30°C .

Example 17

A suspension of 29 g of palladium chloride in 2.9 litres of methanol is hydrogenated in a 10 litre flask. The methanol is decanted and the palladium (sic) black formed is washed first three times with 300 ml of methanol and then three times with 300 ml of ethyl acetate. A solution of 54.5 g of 5,7,3',4'-tetra-O-benzyl-3-O-(2-cyano-ethyl)-(+)-cyanidan-3-ol in 2.9 l of ethyl acetate is then added and hydrogenation is carried out. After the catalyst has been filtered off, the solvent is evaporated off under reduced pressure, the residue is dissolved in 1.5 l of water and the solution is evaporated on a Rotavapor (sic) at 40°C in vacuo to a volume of approximately 500 ml. This procedure is repeated twice and the product is then lyophilized to constant weight. 3-O-(2-Cyano-ethyl)-(+)-cyanidan-3-ol is thus obtained. Yield: 25 g (equal to 94% of theory).

Example 18

56 g of 5,7,3',4'-tetra-O-benzyl-3-(2-cyano-ethyl)-(+)-cyanidan-3-ol, 4 litres of absolute ethanol and 100 ml of chloroform are introduced into a 10 litre flask. The mixture is warmed at 60°C , with exclusion of moisture, until a complete solution is obtained, the solution is then allowed to cool to room temperature and the flask is filled with argon. 25 g of palladium-on-charcoal (10% strength) are added, under argon, and hydrogenation is carried out. Approximately 12 litres of hydrogen are consumed. The hydrogen is then replaced by nitrogen, the catalyst is filtered off and the residue is evaporated under a moderate vacuum. The residue is processed with 1 litre of ethyl acetate and the resulting suspension is stirred at 40°C for 30 minutes. The solvent is evaporated off to a volume of approximately 200 ml, the residue is cooled to approximately 0°C and filtered and the residue is washed with ethyl acetate. The treatment with ethyl acetate is repeated twice and the residue is then washed twice with ethyl acetate and twice with



methylene chloride and dried under a high vacuum at room temperature for 24 hours. The product is taken up in 2 litres of water and the mixture is then concentrated under reduced pressure to a volume of approximately 200 ml. 1.8 litres of water are added and the mixture is again concentrated to a volume of approximately 200 ml. This solution is then lyophilized to constant weight. The hydrochloride of 3-O-(3-aminopropyl)-(+)-cyanidan-3-ol is thus obtained. Melting point = 195°C (with decomposition).

Example 19

5.0 g of sodium hydride (about 55% strength) in an oil suspension are introduced into a 500 ml flask equipped with an ascending condenser, which carries a calcium chloride tube, a feed adapter with pressure compensation, a cannula for introduction of nitrogen, a thermometer and a stirrer. A vigorous stream of nitrogen is allowed to flow through for 5 minutes and the stream of nitrogen is then reduced so that 60 ml of anhydrous tetrahydrofuran can be added dropwise in drops (sic). The mixture is warmed to 40°C by means of an external oil bath and 7.5 ml (17 g) of freshly distilled methyl iodide are then added dropwise, with stirring. A solution of 52.0 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 170 ml of tetrahydrofuran is then added dropwise in the course of one hour. The mixture is left to react for 1 1/2 hours, while stirring, during which the temperature is kept at 40°C. The mixture is cooled to room temperature, 200 ml of water are added and the mixture is stirred for 15 minutes. It is filtered and the filtrate is introduced into a decanting flask containing 200 ml of toluene and 200 ml of water. The organic phases are separated off and washed with 50 ml of water. The aqueous phases are extracted twice with 400 ml of methylene chloride and the combined organic phases are dried over magnesium sulfate and evaporated under a moderate vacuum at 40°C. The residue is dried under 15 mm Hg at 45°C during the night. This residue is taken up in 510 ml of methoxyethanol at 100°C, the mixture is filtered hot and the filtrate is cooled slowly, with stirring. After 8 hours,

he (sic) precipitate formed is filtered off and washed with 30 ml of cold methoxyethanol, which has first been dried at 50°C in vacuo for one night. 5,7,3',4'-Tetra-0-benzyl-3-0-methyl-(+)-cyanidan-3-ol of melting point 124 - 125°C is thus obtained.

Example 20

An aqueous solution of 1.5 litres of 50% strength sodium hydroxide solution, a solution of 52 g of 5,7,3',4'-tetra-0-benzyl-(+)-cyanidan-3-ol in 1.5 litres of butyl chloride and 6.8 g of tetrabutylammonium bisulfate are introduced into a 6 litre flask equipped with a mechanical stirrer and an ascending condenser. The mixture is warmed to 50°C and kept at this temperature for 2 hours 45 minutes, with vigorous stirring. After cooling to room temperature, the two phases are separated and the organic phase is washed three times with 300 ml of water and dried over magnesium sulfate. It is filtered and the butyl chloride is distilled off. The residue is crystallized twice in 3.2 litres of absolute ethanol. After drying, 5,7,3'-4'-0-tetra-benzyl-3-0-butyl-(+)-cyanidan-3-ol of melting point 55 - 56°C is obtained.

Example 21

52 g of 5,7,3',4'-tetra-0-benzyl-(+)-cyanidan-3-ol in 360 ml of anhydrous pyridine are introduced into a 500 ml flask, equipped with a pressure inlet adapter, a condenser which carries a calcium chloride tube, a nitrogen inlet tube and a magnetic stirrer, under nitrogen and while stirring, and 17 g of butyryl chloride are added. The mixture is left to react at room temperature for 5 1/2 hours, with stirring, and 500 ml of water containing pieces of ice are then added. The mixture is stirred for one hour and the oily layer is separated off. This is stirred first with 500 ml of an aqueous solution of sodium bicarbonate (1 N) and then twice with 500 ml of water. The solid product which forms is washed with water and dried in vacuo. The residue is crystallized in a mixture of 3 litres of ethanol and 400 ml of acetone. 5,7,3',4'-Tetra-0-benzyl-3-0-butyryl-(+)-cyanidan-3-

ol, which, after drying, has a melting point of 92 - 93°C, is thus obtained.

Example 22

5,7,3',4'-Tetra-0-benzyl-3-0-(3,3-dimethyl-butanoyl)-(+)-cyanidan-3-ol of melting point 58°C is obtained analogously to Example 21, but using 21.5 g of 3,3-dimethylbutanoyl chloride as the starting substance. The reaction takes one hour.

Example 23

52 g of 5,7,3',4'-tetra-0-benzyl-(+)-cyanidan-3-ol, 400 mg of triethylamine, 80 ml of pyridine and 16 g of succinic anhydride are introduced into a 1 litre flask with a condenser which carries a calcium chloride tube. The mixture is warmed under the reflux condenser for one hour, the solvents are then removed in vacuo at 40°C and the residue is washed twice with 300 ml of water, which has been brought to pH 3 with hydrochloric acid, and then twice with distilled water. The product is crystallized twice in 3 litres of ethanol. 5,7,3',4'-Tetra-0-benzyl-3-0-(3-carboxy-propionyl)-(+)-cyanidan-3-ol of melting point 95 - 96°C is thus obtained.

Example 24

Analogously to Example 21, but in a 1 litre flask and starting from 104 g of 5,7,3',4'-tetra-0-benzyl-(+)-cyanidan-3-ol in 720 ml of pyridine and in the presence of 61 g of caproyl chloride, the mixture is warmed to 50°C in the course of 1 1/2 hours, with stirring, and is then poured onto 3 litres of an ice-water mixture, the mixture is stirred for 1 hour and the precipitate formed is filtered off, washed in (sic) first twice with 1 litre of (1N) aqueous sodium hydroxide solution and then twice with one litre of water and dried in vacuo at room temperature over phosphorus pentoxide. The product is then crystallized from 1.4 l of methoxyethanol and 5,7,3',4'-tetra-0-benzyl-3-0-decanoyl-(+)-cyanidan-3-ol of melting point 88 - 89°C is thus obtained.

Example 25

The procedure followed is as in Example 21, using 44 g of palmitoyl chloride and heating the reaction mixture

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at 90°C in the course of two hours. The resulting 5,7,3',4'-tetra-0-benzyl-3-0-palmitoyl-(+)-cyanidan-3-ol is purified by dissolving in 80 ml of acetone, under the influence of heat, and adding 3 litres of ethanol dropwise to this solution. Melting point = 57 - 59°C.

Example 26

The working out (sic) is as in Example 23, but 24.5 g of tetrahydrophthalic anhydride are used. The reaction mixture is boiled under a reflux condenser for 45 minutes and the solvent is distilled off under a moderate vacuum at 40°C. The residue is taken up in 600 ml of methylene chloride and the mixture is extracted twice with 500 ml of 2 N hydrochloric acid and twice with 500 ml of distilled water. The methylene chloride solution is dried over magnesium sulfate and the solvent is evaporated off. The residue is recrystallized from a mixture of carbon tetrachloride and petroleum ether. 5,7,3',4'-Tetra-0-benzyl-3-0-tetrahydrophthalyl-(+)-cyanidan-3-ol of melting point 67 - 68°C is thus obtained.

Example 27

The procedure followed is as in Example 21, but using 22.5 g of benzoyl chloride, and the reaction mixture is heated at 80°C for 6 hours. The mixture is washed with sodium bicarbonate, whereupon a solid product separates out, and this is crystallized from a mixture of 7 litres of ethanol and 1.25 litres of acetone. 5,7,3',4'-Tetra-0-benzyl-3-0-benzoyl-(+)-cyanidan-3-ol of melting point m.p. 115 - 116°C is thus obtained.

Example 28

The procedure followed is as in Example 21, but using 25.4 g of 4-fluoro-benzoyl chloride. The reaction mixture is kept at room temperature for 7 hours. The solid product is dissolved in 3.5 litres of acetone under the influence of heat and a precipitate is obtained by adding 800 ml of water. 5,7,3',4'-tetra-0-benzyl-3-0-(4-fluoro-benzoyl)-(+)-cyanidan-3-ol of melting point 154°C is thus obtained.

Example 29

The procedure followed is as in Example 21, but using 56.5 g of 3,4-dibenzyloxy-benzoyl chloride in 130 ml of pyridine. The reaction mixture is stirred at room temperature for 2 hours 45 minutes. The resulting solid product is recrystallized twice from acetone. 5,7,3',4'-Tetra-O-benzyl-3-O-(3,4-dibenzyloxy-benzoyl)-(+)-cyanidan-3-ol of melting point 162 - 163°C is thus obtained.

Example 30

The procedure followed is as in Example 21, but using a solution of 32 g of acetylsalicylyl chloride in 180 ml of pyridine. The reaction mixture is stirred at 65°C for 2 hours. After washing with sodium bicarbonate and with water, the solid crude product is crystallized once with 8 litres of ethanol and then with a mixture of 5 litres of ethanol and 1.2 litres of acetone. 5,7,3',4'-Tetra-O-benzyl-3-O-(acetylsalicylyl)-(+)-cyanidan-3-ol of melting point 136 - 137°C is thus obtained.

Example 31

260 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 89 g of phthalic anhydride, 3 litres of triethylamine and 1 litre of pyridine are introduced into a 6 litre flask equipped with a mechanical stirrer, a reflux coil with a calcium chloride tube, a nitrogen inlet adapter and a thermometer. This mixture is boiled (92°C) under the reflux condenser for 9 hours, under nitrogen, and is then allowed to cool to room temperature and is filtered. The mixture is evaporated in vacuo at 40°C on a Rotavapor, the oily residue is taken up in 500 ml of ethylene chloride and the mixture is extracted twice with 500 ml of 2 N aqueous hydrochloric acid and twice with 500 ml of water. The organic solution is dried over magnesium sulfate, filtered and evaporated to dryness. The crude product is recrystallized from 2.5 litres of toluene and 1.6 litres of ligroin. 5,7,3',4'-Tetra-O-benzyl-3-O-(2-carboxy-benzoyl)-(+)-cyanidan-3-ol of melting point 127 - 129°C is thus obtained.

Example 32

The procedure followed is as in Example 21, but the reaction is carried out in a 1 litre flask using 65 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 800 ml of pyridine. The mixture is boiled under nitrogen at 100°C and 17.1 ml (18.7 g) of M-phenyl (sic) isocyanate are added dropwise. The mixture is left at 100°C for 1 hour and then cooled to room temperature and filtered, and 6 litres of water are added, with vigorous stirring, whereupon a white powder forms. The powder is filtered off and the residue is washed with 6 litres of water and dried in vacuo at 60°C for 2 days. It is crystallized from 8 litres of acetone and 5,7,3',4'-tetra-O-benzyl-3-O-(M-phenyl-carbamoyl)-(+)-cyanidan-3-ol (sic) of melting point 204°C is obtained.

Example 33

65 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, dissolved in 500 ml of pyridine and 25 ml of triethylamine, are introduced into a 750 ml flask equipped with a magnetic stirrer, a calcium chloride tube, an inlet adapter and a nitrogen feed. A stream of nitrogen is allowed to flow through, the mixture is cooled to -15°C and 23 g of methanesulfonyl chloride are added in the course of 30 minutes. The reaction mixture is stirred at -15°C for 30 minutes and is then poured onto 2.5 litres of an ice-water mixture, the precipitate is filtered off and stirred with one litre of water and the mixture is filtered. After drying over phosphorus pentoxide, the resulting product is recrystallized from 2 litres of n-butanol, the mixture is filtered and the product is washed with 250 ml of methanol and then with 500 ml of methanol. The substance is dried at room temperature in vacuo over phosphorus pentoxide. 5,7,3',4'-Tetra-O-benzyl-3-O-methanesulfonyl-(+)-cyanidan-3-ol of melting point 138 - 139°C is thus obtained.

Example 34

158 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 250 ml of pyridine are introduced into a 500 ml flask equipped with a reflux condenser, which carries a calcium

chloride tube, a nitrogen feed, a thermometer and a mechanical stirrer. The mixture is warmed to 90°C, whereupon the mixture dissolves, and 67 g of 4-methyl-benzene-sulfonyl chloride are then added hot, and the solution is kept at 90°C for 4 hours, under nitrogen and while stirring. The mixture is then cooled to -30°C and is left to stand for 2 1/2 hours, whereupon a precipitate forms. 1.5 litres of water are added, the mixture is stirred and the precipitate is filtered off, washed with a 1 N solution of aqueous sodium bicarbonate and then with water, until the filtrate is neutral, and recrystallized from 5 litres of chloroform and 20 litres of isopropanol. 5,7,3',4'-Tetra-O-benzyl-3-O-(4-methylbenzenesulfonyl)-(+)-cyanidan-3-ol of melting point 173 - 174°C is thus obtained.

Example 35

First a solution of 300 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 3 litres of toluene and then 4.5 litres of an aqueous solution of sodium hydroxide (50% strength) followed by 16 g of Triton B are introduced, slowly and with stirring, into a 20 litre flask with a decanting ampoule and a mechanical stirrer. Stirring is continued and 82 g of acrylonitrile are then added dropwise in the course of 45 minutes. The mixture is stirred vigorously at room temperature for 2 hours, 30 g of acrylonitrile are then added and stirring is continued for one night. A 3rd portion of 100 g of acrylonitrile is then added. The mixture is stirred for a further 2 hours and the toluene phase is isolated and washed 3 times with 1 litre of 0.1 N hydrochloric acid and then with 2 litres of water. The toluene phase is dried over magnesium sulfate and the toluene is evaporated off. The residue is taken up in 1.8 litres of acetone and this solution is added to 5.4 litres of boiling ethanol, with vigorous stirring. The 5,7,3',4'-tetra-O-benzyl-3-O-(2-cyano-ethyl)-(+)-cyanidan-3-ol precipitates out on cooling and is filtered off and dried. Melting point = 100 - 101°C.

Example 36

52 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 260 ml of anhydrous dioxane and 130 mg of paratoluenesulfonic

acid are introduced into a 500 ml flask equipped with a nitrogen inlet, a feed adapter which is pressure-compensated, a calcium chloride tube and a magnetic stirrer. 26 ml (24 g) of dihydropyran are slowly added to this mixture, with stirring. The mixture is stirred at room temperature for 2 1/2 hours and filtered and the filtrate is evaporated in vacuo. The residue is taken up in 500 ml of chloroform and the resulting solution is washed first twice with 300 ml of a 1 N solution of aqueous bicarbonate and then with 300 ml of distilled water. The chloroform solution is dried over magnesium sulfate, filtered and evaporated. The residue is dried under a high vacuum at room temperature. 5,7,3',4'-Tetra-O-benzyl-3-O-tetrahydropyranyl-(+)-cyanidan-3-ol is thus obtained as a mixture of 2 diastereoisomers. The product is a glutinous mass, the melting point of which cannot be determined.

Example 37

A suspension of 92.8 g of a 55% strength dispersion of sodium hydride in oil (51 g of NaH) in one litre of freshly distilled dimethylformamide is prepared under nitrogen and with thorough stirring. The suspension is cooled to a temperature of between -5 and 0°C and a solution of 145 g of (+)-cyanidan-3-ol in 2 litres of freshly distilled dimethylformamide is added, so that the temperature of the dispersion remains constant. The hydrogen formed is removed by circulating nitrogen.

After the introduction of the (+)-cyanidan-3-ol, the mixture is left to stand at a low temperature for 15 minutes and 276.5 ml of benzyl bromide are then added in the course of 1 1/2 hours so that the temperature does not rise above 0°C. The mixture is left to stand at this temperature for a further half an hour and is then warmed to room temperature.

The dimethylformamide is distilled off in vacuo at 60°C, the oily residue is taken up in 3 litres of trichloroethylene and the organic solution is washed with 3 litres of distilled water and filtered. The filtrate is concentrated and the residue is cooled, and 5,7,3',4'-tetra-

O-benzyl-(+)-cyanidan-3-ol, which crystallizes in the form of white needles, is thus obtained. Melting point = 144 - 145°C.

Example 38

5,7,3',4'-Tetra-O-benzyl-(+)-cyanidan-3-ol is obtained under the same conditions as in Example 37, but using dimethylformamide which has been thoroughly dried.

Example 39

Tetra-O-benzyl-5,7,3',4'-(+)-cyanidan-3-ol is obtained analogously to Example 37, but using 2.25 mol of benzyl chloride.

Example 40

A solution of 1.45 g of (+)-cyanidan-3-ol in 20 ml of freshly distilled dimethyl sulfoxide is added slowly, while stirring and at room temperature, is added (sic) to a solution of 0.93 g of a dispersion of sodium hydride in oil (0.51 g of NaH) in 10 ml of dimethyl sulfoxide, which has been freshly distilled. The hydrogen formed is removed by circulating nitrogen. After the mixture has been stirred at room temperature for one hour, the evolution of nitrogen virtually ceases and the sodium salts (sic) of (+)-cyanidan-3-ol is partly deposited on the wall of the flask. 2.68 ml of benzyl bromide are then added dropwise. The mixture is left to stand at room temperature for 1 1/2 hours, with stirring, and the reaction solution is then introduced slowly and with stirring into 300 ml of a cold aqueous 10% strength solution of sodium chloride. The precipitate is filtered off and dried in vacuo at 80°C and then recrystallized from 40 ml of carbon tetrachloride. 1.96 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol are obtained.

Example 41

The procedure followed is as in Example 37, but 416 g of α -bromo-o-xylene are used instead of benzyl bromide. The residue obtained after evaporation of the dimethylformamide is taken up in chloroform and the solution is washed with distilled water, filtered and evaporated. The residue is crystallized from a mixture of benzene and petroleum ether (6:3 volume/volume). 5,7,3',4'-Tetra-O-(2-methyl-benzyl)-

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(+)-cyanidan-3-ol of melting point 88 - 90°C is thus obtained.

Example 42

5,7,3',4'-Tetra-O-(4-methyl-benzyl)-(+)-cyanidan-3-ol, which melts at 66 - 70°C after recrystallization from carbon tetrachloride, is obtained analogously to Example 37, but using 416 g of α -bromo-p-xylene instead of benzyl bromide.

Example 43

5,7,3',4'-Tetra-O-(2-bromo-benzyl)-(+)-cyanidan-3-ol, which is recrystallized from a mixture of chloroform and carbon tetrachloride (40:55 volume/volume), is obtained analogously to Example 37, but using 562 g of 2-bromobenzyl bromide instead of benzyl bromide. Melting point = 155 - 157°C.

Example 44

5,7,3',4'-Tetra-O-methoxymethyl-(+)-cyanidan-3-ol, which has a melting point of 92 - 93°C after recrystallization from a mixture of water and methanol (1:1 volume/volume), is obtained analogously to Example 37, but using 181 g of chlorodimethyl ether instead of benzyl bromide.

Example 45

5,7,3',4'-Tetra-O-allyl-(+)-cyanidan-3-ol, which has a melting point of 78.5 - 80°C after recrystallization from n-hexane, is obtained analogously to Example 37, but using 272 g of allyl bromide instead of benzyl bromide.

Example 46

5,7,3',4'-Tetra-O-ethoxycarbonyl-(+)-cyanidan-3-ol, the melting point of which is approximately 65°C, is obtained analogously to Example 37, but using 244 g of ethyl chloroformate (sic) instead of benzyl bromide.

Example 47

1.45 g of (+)-cyanidan-3-ol are dissolved in 50 ml of anhydrous acetone, 6.91 g of anhydrous potassium carbonate are added and it (sic) is heated under reflux in nitrogen. A solution of 6.26 g of p-bromo-phenacyl bromide in 30 ml of anhydrous acetone is added to this solution and the mixture is boiled for a further 3 hours, with mechanical stirring.

After the reaction mixture has cooled, the salts are filtered off and the solution is evaporated to dryness. The residue is taken up in 50 ml of chloroform, the chloroform solution is washed 3 times with 50 ml of water, the chloroform is evaporated off, the residue is dissolved in approximately 1,000 ml of ether and the ether solution is filtered and concentrated to 150 ml. 5,7,3',4'-Tetra-O-(4-bromo-phenacyl)-(+)-cyanidan-3-ol, which has a melting point of 127 - 129°C after recrystallization on (sic) ethanol, is thus obtained.

Example 48

5.4 g of sodium hydride in a suspension in oil (55% strength) are introduced, under nitrogen, into a 500 ml flask equipped with a reflux condenser, which carries a calcium chloride tube, a nitrogen inlet and a feed adapter and a magnetic stirrer, the sodium hydride is washed twice with 50 ml of anhydrous hexane to remove the oil and is dried in ~~vacuo~~ and a solution of 32.5 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 200 ml of tetrahydrofuran (anhydrous) is added. The mixture is warmed under reflux for 2 hours and cooled in an ice-bath and a solution of 9 g of methoxymethyl chloride in 40 ml of anhydrous tetrahydrofuran is added dropwise in the course of 45 minutes. The mixture is stirred in the ice-bath for 2.5 hours, the solution is filtered over Cellite and the filtrate is evaporated to dryness at room temperature on a Rotavapor. The residue is crystallized twice from a mixture of 200 ml of acetone and 500 ml of 2-propanol. The resulting 5,7,3',4'-tetra-O-benzyl-3-O-methoxymethyl-(+)-cyanidan-3-ol has a melting point of 108 - 110°C.

Example 49

7.15 g of palladium chloride, suspended in 2.4 litres of methanol, are hydrogenated in a 5 litre flask. The majority of the methanol is decanted off and the palladium is washed 4 times with 4 litres of methanol and 4 times with 200 ml of ethyl acetate. During the last decanting phase, a thin layer of ethyl acetate is left over the palladium. A solution of 20 g of 5,7,3',4'-tetra-O-benzyl-3-O-methoxy-

methyl-(+)-cyanidan-3-ol in 2.4 litres of ethyl acetate is added. Hydrogenation consumes 3.6 litres of hydrogen and takes 5 hours. The palladium is then filtered off and washed twice with 200 ml of ethyl acetate, the combined ethyl acetate solutions are evaporated, 700 ml of ethanol are added to the residue, the mixture is evaporated to approximately 100 ml and this procedure is repeated a second time and then ... (sic) twice with 700 ml of water. The residue is dried to constant weight under a high vacuum at room temperature. 3-O-Methoxymethyl-(+)-cyanidan-3-ol of melting point 106 - 109°C is obtained.

Example 50

42.5 g of boron trifluoroetherate in 50 ml of diglyme freshly distilled over sodium are introduced into a flask A equipped with a nitrogen inlet, an inlet adapter and a vacuum connector. A ... (sic) 7.65 g of sodium borohydride in 250 ml of diglyme is introduced through the feed adapter.

A solution of 28 g of 5,7,3',4'-tetra-O-benzyl-3-O-(2-cyano-ethyl)-(+)cyanidan-3-ol in 500 ml of tetrahydrofuran, which has been freshly distilled over sodium, is introduced into a second flask B equipped with a feed adapter, a cannula connected to the vacuum cannula of flask A, an independent nitrogen feed and an ascending condenser, the top opening of which ... (sic) with a wash bottle containing acetone. The two flasks A and B are equipped with a magnetic stirrer, and flask A is stirred vigorously whilst flask B is stirred gently. A stream of nitrogen is flushed through flask A, flask B, the condenser of flask B and the wash bottle. A solution of sodium borohydride is introduced dropwise into flask A in the course of 1 1/2 hours, whereupon boron hydride is formed and is transported with the nitrogen into flask B. There it reduces the 2-cyano-ethyl grouping to the 3-amino-propyl grouping. When the introduction of sodium borohydride has ended, the mixture is allowed to react for 5 1/2 hours. 100 ml of absolute ethanol are then added through the feed adapter of flask B, evolution of gas being found.

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The contents of flask B are then distilled on a Rotavapor in vacuo at a temperature below 30°C. The residue is taken up in 200 ml of boiling butanol and the mixture is then left to stand at 4°C overnight, whereupon an oil forms. The butanol is decanted and this treatment is repeated 4 times.

The combined butanol extracts are dried on a Rotavapor and the residue is dried to constant weight under a high vacuum over phosphorus pentoxide for 24 hours. The resulting 5,7,3',4'-tetra-O-benzyl-3-O-(3-amino-propyl)-(+)-cyanidan-3-ol has a melting point of 93 - 95°C.

Example 51

A suspension of 65.5 g of a dispersion of sodium hydride in oil (55% strength) in 700 ml of freshly distilled formamide is prepared under nitrogen, with vigorous stirring. This suspension is cooled to -5 to 0°C and a solution of 650 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 3,800 ml of freshly distilled dimethylformamide is slowly added such that the temperature remains between -5 and 0°C. 15 minutes later, 178.5 ml of benzyl bromide are added in the course of approximately 45 minutes such that the temperature always remains below 0°C. This temperature is maintained for a further 30 minutes, the mixture is allowed to warm to room temperature, with stirring, the dimethylformamide is distilled off in vacuo at 60°C on a Rotavapor, the residue is taken up at (sic) 3 litres of chloroform at room temperature and the chloroform solution is then washed 3 times with 2 litres of water, filtered and evaporated. The residue is taken up in 1,750 ml of hot benzene and petroleum ether is added slowly, under the influence of heat and with stirring, until the mixture starts to become cloudy (about 1 litre of petroleum ether is required). After cooling, 3,5,7,3',4'-penta-O-benzyl-(+)-cyanidan-3-ol of melting point 119 - 121°C is obtained.

Example 52

0.96 g of a 55% strength dispersion of sodium hydride on (sic) oil is introduced into a 50 ml flask with a feed adapter,

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a nitrogen feed and a condenser, which carries a calcium chloride tube, and the entire set-up is dried by warming in a stream of nitrogen. After cooling under a gentle stream of nitrogen, 10 ml of freshly distilled dimethyl sulfoxide are introduced and the mixture is stirred at room temperature. A solution of 1.45 g of (+)-cyanidan-3-ol in 15 ml of freshly distilled dimethyl sulfoxide is added dropwise, whereupon hydrogen is evolved. 30 minutes later, a solution of 2.74 ml of methoxyethoxymethyl chloride in 10 ml of dimethyl sulfoxide are added, 30 minutes later the reaction solution is poured into 150 ml of water saturated with sodium chloride and the pH is brought to 7. A glutinous brown-black precipitate is obtained and is extracted 3 times with 100 ml of toluene. The resulting solutions are combined and washed 3 times with 50 ml of water. The toluene is removed and the resulting brown-red oil is extracted under reflux 10 times with 100 ml of n-hexane. The n-hexane solutions give 5,7,3',4'-tetra-0-methoxyethoxymethyl-(+)-cyanidan-3-ol in the form of a yellow oil, which is decomposed at 150°C/0.02 mm Hg.

Example 53

52 g of 5,7,3',4'-tetra-0-benzyl-(+)-cyanidan-3-ol in 300 ml of anhydrous pyridine are introduced into a 500 ml flask equipped with a feed adapter, a condenser, which carries a calcium chloride tube, a nitrogen feed and a magnetic stirrer. The mixture is stirred under nitrogen, 18 g of ethyl chloroformate are added dropwise and the mixture is heated at 60°C for 7 hours. It is allowed to cool and is mixed with 500 ml of ice-water, the precipitate formed is filtered off and mixed with 500 ml of an aqueous 0.5 N solution of sodium bicarbonate and the precipitate is filtered off, washed with water and dried in vacuo overnight. The residue is taken up in 550 ml of acetone and the mixture is then filtered, the filtrate is boiled with 3.3 litres of ethanol under a reflux condenser and the mixture is left to stand at room temperature for 2 days. The precipitate is filtered off and recrystallized from a mixture of 250 ml of acetone and 1.5 litres of ethanol. 5,7,3',4'-Tetra-0-benzyl-

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3-O-ethoxycarbonyl-(+)-cyanidan-3-ol of melting point 83 - 84°C is thus obtained.

Example 54

Palladium black is prepared as in Example 1, starting from 4 g of palladium chloride, and a solution of 15 g of 5,7,3',4'-tetra-O-benzyl-3-O-ethoxycarbonyl-(+)-cyanidan-3-ol in 600 ml of ethyl acetate is added. Hydrogenation is carried out for 2 1/2 hours, whereupon 2.33 litres of hydrogen are consumed. The palladium is filtered off and washed twice with 200 ml of ethyl acetate and the combined ethyl acetate solutions are evaporated to dryness. 500 ml of ethanol are added to the residue, the mixture is evaporated to a volume of approximately 50 ml, 200 ml of ethanol and 250 ml of water are added, the mixture is evaporated again to a volume of 50 ml, 500 ml of water are added and the mixture is evaporated to 50 ml. This operation is repeated and the precipitate is then filtered off and dried to constant weight under a high vacuum. 3-O-Ethoxycarbonyl-(+)-cyanidan-3-ol of melting point 123 - 124°C is thus obtained.

Example 55

A solution of 65 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 350 ml of anhydrous pyridine is introduced into a 750 ml flask equipped with a feed adapter, a condenser coil, which carries a calcium chloride tube, a nitrogen inlet and a magnetic stirrer. The solution is warmed to 60°C, 31 g of phenylacetyl chloride are then added dropwise, while stirring and under nitrogen, and the mixture is allowed to react under the same conditions for 6 hours and, after cooling, is poured onto 1 kg of crushed ice. The mixture is stirred until the ice has melted, the water is decanted and the precipitate is washed twice with 1 litre of a 1N aqueous solution of sodium bicarbonate and then twice with 1 litre of water. The product is dried in vacuo overnight and crystallized in 1.2 litres of ethoxyethanol. The 5,7,3',4'-tetra-O-benzyl-3-O-phenylacetyl-(+)-cyanidan-3-ol thus obtained has a melting point of 83 - 85°C.

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Example 56

6.5 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 1.9 g of 2,4-dinitro-fluorobenzene, 3 g of potassium fluoride, 500 mg of 18-crown-6- (sic) and 100 ml of anhydrous tetrahydrofuran are introduced into a 250 ml flask equipped with a condenser, which carries a calcium chloride tube, a nitrogen feed and a magnetic stirrer. The mixture is boiled under reflux for 24 hours, while stirring and under nitrogen, and is allowed to cool, 250 ml of toluene are added, the mixture is washed 4 times with 300 ml of a saturated aqueous solution of sodium chloride, the organic phase is dried over magnesium sulfate and the solvents are evaporated off in vacuo. The residue is washed twice with 25 ml of petroleum ether and then dissolved in 45 ml of chloroform, and 325 ml of absolute ethanol are slowly added, while boiling. The mixture is allowed to cool, to give an oil which is separated off by decanting. The product is washed with a little ethanol and dried in vacuo in the course of 24 hours. 5,7,3',4'-Tetra-O-benzyl-3-O-(2,4-dinitro-phenyl)-(+)-cyanidan-3-ol of melting point 61 - 62°C is thus obtained.

Example 57

400 mg of sodium hydride (sic) (55% strength dispersion in oil) are introduced into a 50 ml flask, a vigorous stream of nitrogen is allowed to flow in over a period of 5 minutes and 5 ml of anhydrous tetrahydrofuran, which has been freshly distilled over sodium, are added. The mixture is warmed to 40°C and a solution of 0.5 ml of methyl iodide in 10 ml of anhydrous tetrahydrofuran and then a solution of 2.3 g of 5,7,3',4'-tetra-O-methoxymethyl-(+)-cyanidan-3-ol in 10 ml of anhydrous tetrahydrofuran are added. The reaction mixture is stirred at 40°C for 1 hour and then filtered. 20 ml of toluene and 40 ml of water are added to the filtrate and the mixture is shaken and left to settle before the organic phase is separated off. This is washed again with 10 ml of water. The wash waters are extracted with 30 ml of methylene chloride, the organic combined extracts are dried over magnesium sulfate and filtered and the filtrate is then evaporated on

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a Rotavapor. The oil which remains is taken up in 55 ml of methanol, the mixture is treated with active charcoal, the methanol is evaporated, the oil which remains is extracted twice with 25 ml of petroleum ether under the influence of heat and the petroleum ether fractions are combined and evaporated on a Rotavapor at room temperature. The oil thus obtained is 5,7,3',4'-tetra-O-methoxymethyl-3-O-methyl-(+)-cyanidan-3-ol. IR (Nujol) ν (cm^{-1}): 2920, 1615, 1590, 1507, 1494, 1440, 1400, 1260, 1220, 1155, 1070, 1000, 920, 822.

Example 58

110 g of potassium carbonate, under a weak stream of nitrogen, and then 250 ml of dimethylformamide are introduced into a 1 litre flask, and a solution of 20.9 g of (+)-cyanidan-3-ol in 250 ml of dried dimethylformamide and 71.25 ml of benzyl bromide, dissolved in 100 ml of dimethylformamide, are poured in. The mixture is warmed at 100°C for 5 1/2 hours, while stirring and in a stream of nitrogen. The resulting suspension is filtered hot, the filtrate is evaporated at 80°C in vacuo on a Rotavapor and the residue is dissolved in 250 ml of chloroform. The chloroform solution is filtered, washed 3 times with 250 ml of water, dried over magnesium sulfate and evaporated to dryness. The residue is taken up in 750 ml of carbon tetrachloride boiling under reflux and the brown glutinous residue is separated off and left to crystallize at room temperature, with stirring and occasional cooling in a refrigerator. The resulting product is identical to that of Example 37. Melting point = $144 - 145^{\circ}\text{C}$.

Example 59

Palladium black is prepared as described in Example 1, starting from 5 g of palladium chloride, a solution of 40 g of 5,7,3',4'-tetra-O-benzyl-3-O-phenylacetyl-(+)-cyanidan-3-ol in 2.25 litres of ethyl acetate is added, hydrogenation is carried out for 3 days, during which 1.25 litres of hydrogen are consumed, the palladium is filtered off and washed twice with 300 ml of ethyl acetate and the combined acetate solutions are concentrated under reduced pressure. 500 ml of

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ethanol are added to the residue, the solution is evaporated to a volume of approximately 50 ml and this operation is repeated. 250 ml of ethanol and 250 ml of water are then added and the mixture is evaporated to a volume of about 50 ml. 500 ml of water are added, the mixture is again evaporated to about 50 ml in vacuo, 500 ml of water are added and the mixture is evaporated again under reduced pressure. The residue is dried to constant weight overnight. The 3-O-phenyl-acetyl-(+)-cyanidan-3-ol thus obtained has a melting point of 102 - 103°C.

Example 60

A solution of 24.8 g of nicotinoyl chloride and 100 ml of anhydrous pyridine is introduced into a 250 ml flask, 56 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol are then added dropwise in 4 portions (1 of 26 g and 3 of 10 g, each addition being separated by one hour), while stirring and under nitrogen, and the mixture is warmed at 60°C for 20 hours. After cooling, the solution is poured onto 1 kg of crushed ice and stirred until the ice has melted. The glutinous precipitate is decanted off and washed twice with water, twice with 1 N sodium bicarbonate and then twice with water. The insoluble material, which is still glutinous, is dried overnight in vacuo, 120 ml of acetone are added and the mixture is stirred for 10 minutes and left to stand at -30°C for 2 hours. The precipitate is filtered off and treated again with acetone. The 5,7,3',4'-tetra-O-benzyl-3-O-nicotinoyl-(+)-cyanidan-3-ol has a melting point, after recrystallization from 950 ml of methoxyethanol and 1.9 litres of anhydrous ethanol, of 137 to 138°C.

Example 61

1.5 g of 5,7,3',4'-tetra-O-benzyl-3-O-nicotinoyl-(+)-cyanidan-3-ol are hydrogenated in the presence of 100 ml of anhydrous ethanol, 300 mg of trifluoromethanesulfonic acid and 1.0 g of palladium-on-active charcoal (10% strength) by warming the mixture to 50°C. The reaction takes 5 hours and consumes 500 ml of hydrogen. The mixture is cooled and then filtered and the filtrate is evaporated to dryness.



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100 ml of distilled water are added to the residue, the mixture is then evaporated to about 10 ml, this operation is repeated three times and the product is lyophilized. The trifluoromethanesulfonate of 3-O-(3-piperidine-carbonyl)-(+)-cyanidan-3-ol of melting point 125 - 130°C is thus obtained. (Mixture of 2 diastereomers).

Example 62

5.2 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 200 ml of toluene are introduced into a 500 ml flask equipped with a reflux condenser and a vibromixer. The mixture is warmed to about 90°C, until a solution is obtained, and 200 ml of a 50% strength solution of sodium hydroxide, 2.7 g of tetrabutylammonium bisulfate and 3.0 g of 2-cyclohexyl-ethylbromide are then added. The mixture is kept at 90°C for 10 hours, with thorough stirring, 1.5 g of 2-cyclohexyl-ethyl bromide are then added, the mixture is stirred at 90°C for a further 15 hours, the reaction mixture is then cooled to room temperature, the two phases are separated, the organic phases are washed 3 times with 250 ml of water and the toluene is dried over magnesium sulfate. The mixture is evaporated, the residue is taken up in 60 ml of absolute ethanol at 60°C and the mixture is stirred for 15 minutes and filtered hot. The insoluble portion is dried in vacuo and recrystallized from 80 ml of methoxyethanol. 5,7,3',4'-Tetra-O-benzyl-3-O-(2-cyclohexyl-ethyl)-(+)-cyanidan-3-ol of melting point = 110°C is thus obtained.

Example 63

1.0 g of 5,7,3',4'-tetra-O-benzyl-3-O-(2-cyclohexyl-ethyl)-(+)-cyanidan-3-ol in 90 ml of methyl acetate is hydrogenated in the presence of 400 mg of palladium (10% strength)-on-active charcoal. 180 ml of hydrogen are consumed. The mixture is filtered, the solvent is evaporated off, the residue is dissolved in 100 ml of ethanol, the solution is evaporated almost to dryness, 100 ml of ethanol are added and the mixture is then evaporated again. 50ml of ethanol and 50 ml of water are added and the mixture is evaporated. The residue is taken up in 150 ml of water, the mixture is

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evaporated to dryness and the residue is dried to constant weight over phosphorus pentoxide under a high vacuum. 3-O-(2-Cyclohexyl-ethyl)-(+)-cyanidan-3-ol of melting point 99 - 102°C is thus obtained.

Example 64

65 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 2 litres of toluene are introduced into a 6 litre flask with a reflux condenser and a mechanical stirrer. The mixture is warmed until a solution is obtained and 1.5 litres of a 50% strength sodium hydroxide solution, 34 g of tetrabutylammonium bisulfate and 40 g of 3-phenyl-propyl bromide are then added. The mixture is warmed at 50°C at (sic) 40 hours, with thorough stirring, and after cooling to room temperature, the two phases are separated and the organic phase is washed 3 times with one litre of water. The toluene is dried over magnesium sulfate and evaporated. The oily residue is washed with 200 ml of petroleum ether and then with 150 ml of anhydrous ethanol and the product is recrystallized from 600 ml of methoxy-ethanol. 5,7,3',4'-Tetra-O-benzyl-3-O-(3-phenyl-propyl)-(+)-cyanidan-3-ol of melting point = 96 - 97°C is obtained.

Example 65

40.0 g of 5,7,3',4'-tetra-O-benzyl-3-O-(3-phenyl-propyl)-(+)-cyanidan-3-ol, dissolved in 3 litres of ethyl acetate, are hydrogenated in the presence of 16 g of palladium-on-charcoal (10% strength). The reaction takes 6 hours and consumes 6.2 litres of hydrogen. The mixture is filtered, the solvent is evaporated off, 250 ml of water are added and the mixture is shaken and evaporated in vacuo until heavy precipitation occurs. The mixture is filtered and the precipitate is washed thoroughly with water to give 3-O-(3-phenyl-propyl)-(+)-cyanidan-3-ol of melting point 190 - 192°C.

Example 66

52 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 500 ml of toluene are introduced into a 3 litre flask which has a reflux condenser and a mechanical stirrer. The mixture is warmed until a solution is obtained, and 187 g of



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propyl chloride, 750 ml of sodium hydroxide (50% strength) and 6.8 g of tetrabutylammonium bisulfate are added. The mixture is warmed to 50°C, stirred thoroughly for 24 hours and then allowed to cool to room temperature. The two phases are separated and the organic phase is washed 3 times with 500 ml of a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated. 100 ml of carbon tetrachloride are added to the residue and the mixture is evaporated to dryness. The resulting 5,7,3',4'-tetra-O-benzyl-3-O-propyl-(+)-cyanidan-3-ol has a melting point, after recrystallization from a mixture of 1.8 litres of ethanol and 0.3 litre of acetone, of 92 - 93°C.

Example 67

Palladium black is prepared from 12 g of palladium chloride as in Example 1 and a solution of 41.6 g of 5,7,3',4'-tetra-O-benzyl-3-O-propyl-(+)-cyanidan-3-ol in 1.8 litres of ethyl acetate is added. Hydrogenation is carried out for 6 hours and 6.25 litres of hydrogen are consumed. The mixture is filtered, the palladium is washed twice with 200 ml of ethyl acetate, the combined solutions are evaporated, 500 ml of water are added to the residue and it (sic) is evaporated under reduced pressure to a volume of approximately 50 ml. This operation is repeated 3 times and the product is then lyophilized. 3-O-Propyl-(+)-cyanidan-3-ol of melting point 94 - 96°C is thus obtained.

Example 68

A solution of 65.0 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 500 ml of anhydrous pyridine is introduced into a 1 litre flask equipped with a reflux condenser, which carries a calcium chloride tube, a feed adapter with pressure compensation, a stirrer and a nitrogen inlet. 34.5 g of diethyl chlorophosphate are added dropwise, under nitrogen, and the mixture is stirred at room temperature for 8 hours, under nitrogen. The reaction mixture is then poured onto 1 litre of ice-water and thoroughly mixed intensively. The water is decanted off from the glutinous mass and the latter is washed 5 times with 500 ml of water and left to stand at 40°C in



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vacuo for one night. The resulting product is recrystallized from 720 ml of carbon tetrachloride and 2.8 ... (sic) of petroleum ether. 2R,3S-5,7,3',4'-Tetra-benzyloxy-3-flavanyl diethyl phosphate of melting point 96°C is thus obtained.

Example 69

Palladium black is prepared as described in Example 1, starting from 13 g of palladium chloride, a solution of 30.0 g of 2R,3S-5,7,3',4'-tetra-benzyloxy-3-flavanyl diethyl phosphate in 1.3 litres of ethyl acetate is added and hydrogenation is carried out for 3 hours, 3.9 litres of hydrogen being consumed. The palladium is filtered off and washed twice with 200 ml of ethyl acetate, the combined solutions are concentrated, 750 ml of water is added to the residue and the mixture is evaporated again under reduced pressure to a volume of approximately 100 ml. This procedure is repeated twice and the product is lyophilized. 2R,3S-5,7,3',4'-Tetra-hydroxy-3-flavanyl (sic) of melting point 121 - 123°C is thus obtained.

Example 70

1,3 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 100 ml of toluene, 100 ml of an aqueous 50% strength solution of sodium hydroxide, 500 mg of dimethyl sulfate and 68 mg of tetrabutylammonium bisulfate are introduced into a 500 ml flask with a discharge condenser and a Mechanical (sic) stirrer. The mixture is warmed at 50°C for one hour and stirred vigorously, and it is then allowed to cool to room temperature and the two phases are separated. The organic phase is washed 3 times with 100 ml of water, dried over magnesium sulfate and evaporated. The resulting 5,7,3',4'-tetra-O-benzyl-3-O-methyl-(+)-cyanidan-3-ol is crystallized from 13 ml of methoxyethanol and has a melting point of 124 - 125°C.

Example 71

500 mg of palladium black, 120 ml of ethanol, 650 mg of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 60 ml of cyclohexene are introduced into a 250 ml flask. The reaction mixture is boiled under reflux for 4 hours, while stirring,

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the palladium is filtered off at room temperature and the filtrate is distilled under reduced pressure. The (+)-cyanidan-3-ol which remains has a melting point, after recrystallization from water, of 207 - 210°C.

Example 72

A 500 ml flask is equipped with a mechanical stirrer, a feed adapter, a calcium chloride tube and a feed for nitrogen. The entire system is dried and (sic) placed under nitrogen, before 100 ml of anhydrous dimethylformamide are added. The dimethylformamide is cooled to -3°C, 9.28 g of an oily dispersion of sodium hydride (55% strength) are added, followed by a solution of 14.5 .. (sic) of (+)-cyanidan-3-ol in 200 ml of anhydrous dimethylformamide and 1.698 g of tetra-n-butylammonium bisulfate, with vigorous stirring, and the mixture is stirred at 0°C for 1 hour. A solution of 25.9 ml of benzyl chloride in 25 ml of anhydrous dimethylformamide is then added in the course of 15 minutes and the mixture is stirred at 0°C for 30 minutes. The temperature is allowed to rise to room temperature, the reaction mixture is stirred vigorously for 24 hours and filtered and the filtrate is evaporated under reduced pressure. The residue is taken up in 250 ml of chloroform and the solution is washed 4 times with 250 ml of distilled water, dried over magnesium sulfate, filtered and evaporated. The residue is washed with 50 ml of hexane and then brought to constant weight. This mass is dissolved hot in 500 ml of carbon tetrachloride, the solution is filtered hot and by cooling to room temperature and subsequent concentration to 350 ml and 150 ml, 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, which is identical to the product obtained in Example 37 ... (sic).

Example 73

As in Example 58, after introduction of the cyanidanol solution, 13.22 g of 18-crown-6 are added and the benzyl bromide is replaced by 69 ml of benzyl chloride. The mixture is then warmed at 60°C in the course of 20 hours, with vigorous stirring. 5,7,3',4'-Tetra-O-benzyl-(+)-cyanidan-3-ol, which is identical to the product obtained in Example 37,

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is thus obtained.

Example 74

The procedure followed is analogous to Example 73, but the 18-crown-6 is replaced by 16.98 g of tetra-n-butylammonium bisulfate. 44.5 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol are obtained.

Example 75

130 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 250 g of 1-heptyl chloride and 25 g of tetrabutylammonium bisulfate are introduced into a 5 litre flask with a reflux condenser and a mechanical stirrer. 3.75 litres of a solution of sodium hydroxide (50% strength) are added, the mixture is warmed at 50°C for 6 hours and allowed to cool to room temperature, 1.25 litres of methylene chloride are added and the two phases are separated. The organic phase is washed 3 times with 750 ml of water and dried over magnesium sulfate, the solvent is evaporated off, 4 litres of petroleum ether are then added and the mixture is stirred overnight. The mixture is cooled to -20°C in the course of half an hour and the precipitate is filtered off, washed with 500 ml of petroleum ether and crystallized twice in a mixture of 1.5 litres of ethanol and 400 ml of ethyl acetate. 5,7,3',4'-Tetra-O-benzyl-O-heptyl-(+)-cyanidan-3-ol of melting point 65°C is thus obtained.

Example 76

52 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol and 650 ml of toluene are introduced into a 3 litre flask with a reflux condenser and a mechanical stirrer. The mixture is boiled, until a solution is obtained, and 115 g of 1-chloro-dodecane, 27 g of tetrabutylammonium bisulfate and 750 ml of a 50% strength sodium hydroxide solution are then added. The mixture is warmed at 50°C for 4 days, with vigorous stirring, and is cooled to room temperature, the two phases are separated and the organic phase is washed 3 times with 500 ml of water. It is dried over magnesium sulfate, the solvent is evaporated off and the residue is mixed twice with 500 ml of petroleum ether. After filtration and drying,

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the resulting product is crystallized from 800 ml of acetone and 3.2 litres of ethanol. 5,7,3',4'-Tetra-O-benzyl-3-O-dodecyl-(+)-cyanidan-3-ol of melting point 98 - 99°C is thus obtained.

Example 77

A mixture of 26 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 73 g of 1-chloro-hexadecane and 5 g of tetrabutylammonium bisulfate is introduced into a 1 litre flask with a condenser and a mechanical stirrer. 750 ml of an aqueous sodium hydroxide solution (50% strength) are added and the mixture is warmed at 50°C for 24 hours, with vigorous stirring. After cooling to room temperature, 250 ml of methylene chloride are added, the two phases are separated and the organic phase is washed with 250 ml of water. The solvent is evaporated off, 350 ml of ethanol are added and the mixture is stirred for 2 hours. It is cooled to -10°C and filtered and the residue is washed with 50 ml of ethanol and dried in vacuo. The resulting 5,7,3',4'-tetra-O-benzyl-3-O-hexadecyl-(+)-cyanidan-3-ol has a melting point, after recrystallization from 300 ml of ethanol and 70 ml of ethyl acetate, of 88 - 89°C.

Example 78

52 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol, 162 g of 1-chloro-octadecane and 10 g of tetrabutylammonium bisulfate are introduced into a 3 litre flask with a mechanical stirrer and a reflux condenser. 1.5 litres of a 50% strength solution of sodium hydroxide are added, the mixture is warmed at 50°C for 28 hours, with thorough stirring, and, after cooling to room temperature, 500 ml of methylene chloride are added and the two phases are separated. The organic phase is washed with 500 ml of water, whereupon an emulsion forms. The two phases are separated by filtration over paper can be used for separation (sic), and the organic phase is dried over magnesium sulfate and evaporated. 750 ml of ethanol are added, the mixture is stirred for 2 hours and filtered and the residue is washed with 100 ml of ethanol. The resulting 5,7,3',4'-tetra-O-benzyl-3-O-octadecyl-(+)-

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cyanidan-3-ol has a melting point, after recrystallization from 600 ml of ethanol and 260 ml of ethyl acetate (twice) of 86°C.

Example 79

56 g of 5,7,3',4'-tetra-0-benzyl-3-0-heptyl-(+)-cyanidan-3-ol, dissolved in 2.25 litres of ethyl acetate, are hydrogenated in a 5 litre flask in the presence of 40 g of palladium-on-charcoal (10% strength) and the catalyst is filtered off and washed twice with 300 ml of ethyl acetate. The combined solutions are evaporated, the residue is stirred thoroughly with 250 ml of water and the water is then evaporated off down to a volume of 50 ml. This procedure is repeated twice and the mixture is then evaporated under a high vacuum over phosphorus pentoxide. 3-0-Heptyl-(+)-cyanidan-3-ol of melting point 157 - 159°C is thus obtained.

Example 80

40 g of 5,7,3',4'-tetra-0-benzyl-3-0-dodecyl-(+)-cyanidan-3-ol, dissolved in 3 litres of ethyl acetate, are hydrogenated in a 6 litre flask in the presence of 20 g of palladium-on-charcoal (10% strength). The reaction takes 6 hours and consumes 6.2 litres of hydrogen. The catalyst is filtered off and washed twice with 300 ml of ethyl acetate, the combined solutions are evaporated to dryness and the oily residue is taken up in 1 litre of ethanol. The mixture is concentrated to a volume of 50 ml, one litre of water is added, the mixture is concentrated again to 50 ml, 1 litre of water is then added, the mixture is concentrated to a volume of 100 ml and filtered and the residue is washed with water. Drying under a high vacuum over phosphorus pentoxy (sic) gives 3-0-dodecyl-(+)-cyanidan-3-ol of melting point 158 - 160°C.

Example 81

26.3 g of 5,7,3',4'-tetra-0-benzyl-3-0-hexadecyl-(+)-cyanidan-3-ol, dissolved in 15 litres of ethyl acetate, are hydrogenated in a 3 litre flask in the presence of 16 g of palladium-on-charcoal (10%) and the catalyst is filtered off and washed twice with 100 ml of ethyl acetate. The combined

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solutions are evaporated, the residue is taken up in 100 ml of ether and the mixture is treated with 5 g of active charcoal for one hour. The mixture is filtered, the filtrate is evaporated, the residue is stirred thoroughly with 60 ml of water and the mixture is evaporated to a volume of 10 ml. This procedure is repeated twice and the mixture is then evaporated to dryness and the residue is dried to constant weight under a high vacuum over phosphorus pentoxide. 3-O-Hexadecyl-(+)-cyanidan-3-ol of melting point 152 - 154°C is thus obtained.

Example 82

83.7 g of 5,7,3',4'-tetra-O-benzyl-3-O-octadecyl-(+)-cyanidan-3-ol, dissolved in 4.5 litres of ethyl acetate, are hydrogenated in an 8 litre flask in the presence of 48 g of palladium-on-charcoal (10% strength). The catalyst is filtered off and washed twice with 400 ml of ethyl acetate, the combined solutions are evaporated and the residue is recrystallized from 260 ml of chloroform containing 4% of methanol. The solid residue is treated with 100 ml of water and the mixture is then evaporated to a volume of approximately 25 ml. This procedure is repeated twice, and finally the mixture is evaporated to dryness and the residue is dried to constant weight under a high vacuum over phosphorus pentoxide. 3-O-Octadecyl-(+)-cyanidan-3-ol of melting point 162 - 164°C is thus obtained.

Example 83

A solution of 52 g of 5,7,3',4'-tetra-O-benzyl-(+)-cyanidan-3-ol in 300 ml of methylene chloride, 150 ml of an aqueous 50% strength sodium hydroxide solution and 6.8 g of tetrabutylammonium bisulfate are introduced into a 750 ml flask with a reflux condenser and a mechanical stirrer. The mixture is boiled under reflux for 24 hours, with thorough stirring, and is then cooled to room temperature and the two phases are separated. The organic phase is washed 3 times with 300 ml of water and then dried over magnesium sulfate. The solvent is evaporated off and the resulting di-(5,7,3',4'-tetra-O-benzyl-(+)-cyanidanyl-3-oxy)-methane is recrystal-

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lized from a mixture of 2.4 litres of ethanol and 1.2 litres of acetone. Melting point = 103 - 104°C.

Example 84

Palladium black is prepared as described in Example 1, starting from 5 g of palladium chloride, and a solution of 31.0 g of di-(5,7,3',4'-tetra-O-benzyl-(+)-cyanidanyl-3-oxy)-methane in 700 ml of ethyl acetate is added. Hydrogenation is carried out for 3 hours, 4.8 litres of hydrogen being consumed. The palladium is filtered off and washed twice with 100 ml of ethyl acetate and the combined solutions are evaporated. 1 litre of water, which has been brought to pH 7 with a few drops of pyridine, is added to the residue, the mixture is concentrated to about 100 ml under reduced pressure, this procedure is repeated twice, 900 ml of pure water are then added and the mixture is evaporated to a volume of 200 ml. The product is lyophilized to give di-(cyanidan-3-yl-oxy)-methane of melting point 162 - 165°C.

Example 85

3,5,7,3',4'-Penta-O-methoxymethyl-(+)-cyanidan-3-ol, 3,5,7,3',4'-penta-O-allyl-(+)-cyanidan-3-ol, 5,7,3',4'-tetra-O-trimethylsilyl-(+)-cyanidan-3-ol, 5,7,3',4'-tetra-O-benzyl-3-O-(3-N,N-dimethylamino-propyl)-(+)cyanidan-3-ol, 3-O-(3-N,N-dimethylamino-propyl)-(+)cyanidan-3-ol, in the form of its hydrochloride, 5,7,3',4'-tetra-O-benzyl-3-O-4,4-ethylenedioxy-p-fluorophenyl-butyl)-(+)cyanidan-3-ol, 3-O-(4,4-ethylenedioxy-4-p-fluorophenyl-butyl)-(+)cyanidan-3-ol, 5,7,3',4'-tetra-O-benzyl-3-O-(2,3-dihydroxy-propyl)-(+)cyanidan-3-ol and 3-O-(2,3-dihydroxy-propyl)-(+)cyanidan-3-ol are obtained in an analogous manner to those (sic) in the example described above.

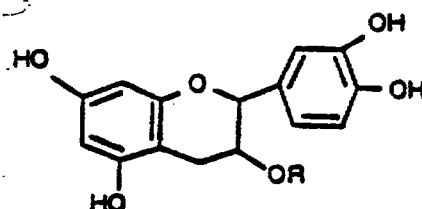


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Patent Claims

1. New O-substituted derivatives of (+)-cyanidan-3-ol of the formula I



(I)

wherein R can be an alkyl or alkenyl radical which is unsubstituted or substituted by hydroxyl, lower alkanoyloxy, lower alkyloxy, lower alkanoyl, cyano, amino, mono- or di-lower alkyl-amino, lower alkyleneamino, oxa- or aza-lower alkylene-amino, carbamoyl, mono- or di-lower alkyl-carbamoyl or halogen atoms, or can be a cycloalkyl radical which has 3 to 6 ring carbon atoms and is unsubstituted or substituted by one or more radicals from the group comprising hydroxyl-, lower alkoxy, lower alkyl, carboxyl, oxo, lower alkanoyl, amino, mono- or di-alkyl-amino or carbo-lower alkoxy, or can be a cycloalkyl-lower alkyl radical, which has 3 to 6 carbon atoms in the ring and can be unsubstituted or substituted by at least one lower alkyl radical, or can be a phenyl or naphthyl radical, which can be Mono- (sic), di- or trisubstituted by hydroxyl, lower alkoxy, carboxyl, carbo-lower alkoxy, nitro, amino- (sic), mono- or di-lower alkylamino or halogen atoms, or can be a phenyl- or naphthyl-lower alkyl or -lower alkenyl radical, which can be mono-, di- or trisubstituted in the aromatic nucleus by hydroxyl, lower alkoxy, carboxyl, carbo-lower alkoxy, alkanoyl, nitro, amino, mono- or dialkyl-amino, di-lower alkyl-carbamoyl or halogen atoms (excluding trihydroxy), or can be a saturated or unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diaza-cyclic radical, which can be fused onto a phenyl nucleus, has 2-7 carbon atoms in the heterocyclic ring and can be mono-, di- or polysubstituted by



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alkyl, hydroxyl, lower alkoxy, nitro, carboxyl, carbo-lower alkoxy or alkanoyloxy, or can be a heterocyclyl-lower alkyl radical, the heterocyclic radical of which is a saturated or unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diaza-cyclic radical, or can be a radical of an alkanecarboxylic acid with at least 3 carbon atoms, lower alkenecarboxylic acid, lower alkanedicarboxylic acid or lower alkenedicarboxylic acid, or can be a cycloalkanecarboxylic acid radical which is unsubstituted or substituted by one or more radicals from the group comprising hydroxyl, lower alkyloxy, carboxyl, carbo-lower alkoxy, lower alkyl, lower alkanoyl, oxo and halogen, or can be ... (sic) benzoyl or naphthoyl radical, which can optionally be substituted by a hydroxyl, lower alkoxy, alkanoyloxy, carboxyl, carbo-lower alkoxy, nitro, amino or halogen radical, or can be a phenyl- or naphthyl-lower alkanoyl radical, which can be unsubstituted in the aromatic part or substituted by hydroxyl, lower alkoxy, carboxyl, carbo-lower alkoxy, lower alkanoyl, lower alkanoyloxy, nitro, amino, mono (sic) or di-lower alkylamino or halogen, or can be a radical of an aza-, thia-, oxa-, thiaza-, oxaza (sic) or diaza-cyclic acid, which can be saturated or unsaturated or can also be fused onto a phenyl radical, or can be an alkoxycarbonyl radical, or can be a phenyloxy-carbonyl radical, or can be a carbamoyl radical, which can optionally be mono- or disubstituted by lower alkyl radicals or phenyl or benzyl radicals, which can optionally be substituted in the ring by hydroxyl, lower alkoxy, lower alkanoyloxy or halogen atoms, or can be a radical of a lower alkyl-sulfonic acid or phenylsulfonic acid, which can be substituted in the ring by lower alkyl, lower alkoxy or halogen atoms, or can be the radical of a phosphoric acid which is unsubstituted or esterified by 1 or 2 lower alkyl or 1 or 2 phenyl radicals, lower denoting a radical with up to 7 C atoms, and their salts.

2. 3-O-Methyl-(+)-cyanidan-3-ol.
3. 3-O-Butyl-(+)-cyanidan-3-ol.
4. 3-O-Butyryl-(+)-cyanidan-3-ol.



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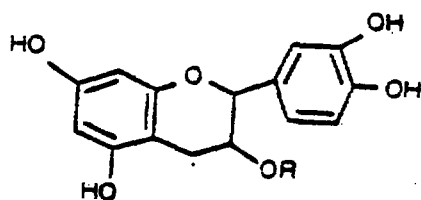
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5. 3-0-(3,3-Dimethyl-butanoyl)-(+)-cyanidan-3-ol.
6. 3-0-(3-Carboxy-propionyl)-(+)-cyanidan-3-ol.
7. 3-0-Decanoyl-(+)-cyanidan-3-ol.
8. 3-0-Dodecyl-(+)-cyanidan-3-ol.
9. 3-0-Heptyl-(+)-cyanidan-3-ol.
10. 3-0-Octadecyl-(+)-cyanidan-3-ol.
11. 3-0-Palmitoyl-(+)-cyanidan-3-ol.
12. 3-0-(2-Carboxy-cyclohexane-carbonyl)-(+)-cyanidan-3-ol.
13. 3-0-Benzoyl-(+)-cyanidan-3-ol.
14. 3-0-(4-Fluoro-benzoyl)-(+)-cyanidan-3-ol.
15. 3-0-Protocatechyl-(+)-cyanidan-3-ol.
16. 3-0-Acetylsalicylyl-(+)-cyanidan-3-ol.
17. 3-0-(2-Carboxy-benzoyl)-(+)-cyanidan-3-ol.
18. 3-0-(N-phenylcarbamoyl)-(+)-cyanidan-3-ol.
19. 3-0-Methanesulfonyl-(+)-cyanidan-3-ol.
20. 3-0-(4-Methyl-benzenesulfonyl)-(+)-cyanidan-3-ol.
21. 3-0-(2-Cyano-ethyl)-(+)-cyanidan-3-ol.
22. 3-0-(3-Amino-propyl)-(+)-cyanidan-3-ol.
23. 3-0-Methoxymethyl-(+)-cyanidan-3-ol.
24. 3-0-Ethoxycarbonyl-(+)-cyanidan-3-ol.
25. Pharmaceutical compositions, characterized in that they contain a compound according to claim 1 or a pharmaceutically usable salt thereof and at least one pharmaceutical excipient.
26. Pharmaceutical compositions, characterized in that they contain a compound according to one of claims 2 - 24 or a pharmaceutically usable salt thereof and at least one pharmaceutical excipient.
27. Use of a compound according to claim 1 as an active compound for the preparation of a medicament for the treatment of liver diseases.
28. Use of a compound according to one of claims 2 - 24 as an active compound for the preparation of a medicament for the treatment of liver diseases.
29. Process for the preparation of O-substituted derivatives of (+)-cyanidan-3-ol of the formula I



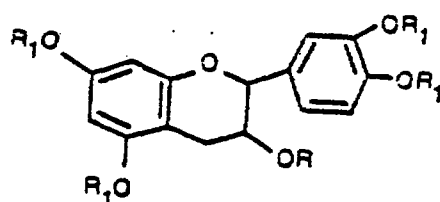
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(I)

wherein R has the meaning given in claim 1, and their salts, characterized in that, in a compound of the formula II



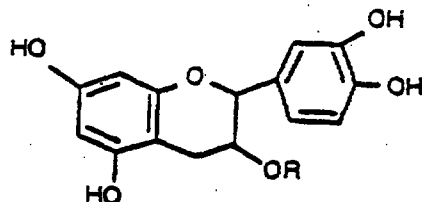
(II)

wherein R^1O represents a protected hydroxyl group which can easily be hydrolysed or hydrogenolysed and R has the above-mentioned meaning, the radical OR^1 is split to give the hydroxyl group and, if desired, a radical R in a resulting compound is converted by reduction, and/or in that a resulting salt is converted into the free compound or a free compound with salt-forming groups is converted into a salt.



Claims (as printed)

1. A novel O-substituted derivative of (-)-cyanidan-3-ol of the formula I



(I)

wherein R is

— an alkyl or alkenyl radical which is unsubstituted or substituted by hydroxy, lower alkanoyloxy, lower alkoxy, lower alkanoyl, cyano, amino, mono- or di-lower alkylamino, lower alkyleneamino, oxa- or aza-lower alkyleneamino, carbamoyl, mono- or di-lower alkylcarbamoyl or by halogen atoms;

— a cycloalkyl radical containing from 3 to 6 ring carbon atoms which is unsubstituted or substituted by one or more hydroxy, lower alkoxy, lower alkyl, carboxy, oxo, lower alkanoyl amino, mono- or di-lower alkylamino or lower alkoxycarbonyl groups;

— a cycloalkyl-lower alkyl radical containing from 3 to 6 ring carbon atoms which is unsubstituted or substituted by at least one lower alkyl group;

— a phenyl or naphthyl radical which may be substituted by one, two or three hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, nitro, amino or mono- or di-lower alkylamino groups, or by one, two or three halogen atoms;

— a phenyl-lower alkyl or naphthyl-lower alkyl radical or phenyl-lower alkenyl or naphthyl-lower alkenyl radical which may be substituted in the aromatic nucleus by one, two or three hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, lower alkanoyl, nitro, amino, mono- or di-lower alkylamino, di-lower alkylcarbamoyl groups or by one, two or three halogen atoms (except trihydroxy);

— a saturated or unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diazacyclic radical which may be fused to a phenyl nucleus and contains from 2 to 7 carbon atoms in the heterocyclic ring, and which may be substituted by one, two or more lower alkyl, hydroxy, lower alkoxy, nitro, carboxy, lower alkoxy-carbonyl or lower alkanoyloxy groups;

— a heterocyclic-lower alkyl radical the heterocycle of which is a saturated or unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diazacyclic radical; a radical of an alkanecarboxylic acid containing at least 3 carbon atoms, lower alkenecarboxylic acid, a lower alkanedicarboxylic acid or a lower alkene-dicarboxylic acid; a lower cycloalkanecarboxylic acid which is unsubstituted or substituted by one or more hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, lower alkyl, lower alkanoyl or oxo groups or halogen atoms;

— a benzoyl or naphthoyl radical which may be substituted by hydroxy, lower alkoxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, nitro or amino groups or by halogen atoms;

— a phenyl- or naphthyl-lower alkanoyl radical which is unsubstituted or substituted in the aromatic nucleus by hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, lower alkanoyl, lower alkanoyloxy, nitro, amino or mono- or di-lower alkylamino or by halogen;

— a radical of an unsaturated aza-, thia-, oxa-, thiaza-, oxaza- or diaza-cyclic acid which may be fused to a phenyl radical; a lower alkoxycarbonyl radical; a phenoxycarbonyl radical; a carbamoyl radical which may be substituted by one or two lower alkyl phenyl or benzyl radicals which may be substituted in the ring by hydroxy, lower alkoxy groups or by halogen atoms;

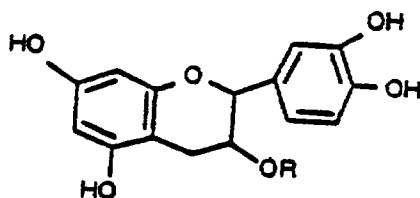
— a radical of a lower alkylsulphonic acid or phenylsulphonic acid which may be substituted in the ring by one or more lower alkyl or lower alkoxy groups or by halogen atoms; or

— a radical of a phosphonic acid which is unsubstituted or esterified by one or two lower alkyl radicals or by one or two phenyl radicals, the term "lower" signifying a radical containing 1 to 7 carbon atoms, or a salt thereof.



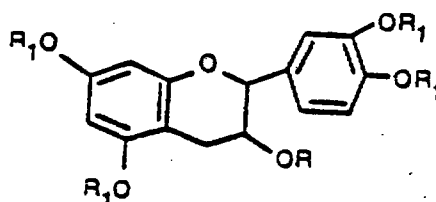
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2. (-) 3-O-Methyl-cyanidan-3-ol.
3. (+) 3-O-Butyl-cyanidan-3-ol.
4. (-) 3-O-Butyryl-cyanidan-3-ol.
5. (+) 3-O-(3,3-Dimethylbutanoyl)-cyanidan-3-ol.
6. (+) 3-O-(3-Carboxypropionyl)-cyanidan-3-ol.
7. (+) 3-O-Decanoyl-cyanidan-3-ol.
8. (+) 3-O-Dodecyl-cyanidan-3-ol.
9. (+) 3-O-Heptyl-cyanidan-3-ol.
10. (+) 3-O-Octadecyl-cyanidan-3-ol.
11. (+) 3-O-Palmitoyl-cyanidan-3-ol.
12. (+) 3-O-(2-Carboxycyclohexanecarbonyl)-cyanidan-3-ol.
13. (+) 3-O-Benzoyl-cyanidan-3-ol.
14. (+) 3-O-(4-Fluorobenzoyl)-cyanidan-3-ol.
15. (+) 3-O-Protocatechyl-cyanidan-3-ol.
16. (+) 3-O-(Acetylsalicylyl)-cyanidan-3-ol.
17. (+) 3-O-(2-Carboxybenzoyl)-cyanidan-3-ol.
18. (+) 3-O-(N-Phenylcarbamoyl)-cyanidan-3-ol.
19. (+) 3-O-Methanesulphonyl-cyanidan-3-ol.
20. (+) 3-O-(4-Methylbenzenesulphonyl)-cyanidan-3-ol.
21. (+) 3-O-(2-Cyanoethyl)-cyanidan-3-ol.
22. (+) 3-O-(3-Aminopropyl)-cyanidan-3-ol.
23. (+) 3-O-Methoxymethyl-cyanidan-3-ol.
24. (+) 3-O-Ethoxycarbonyl-cyanidan-3-ol.
25. A pharmaceutical composition which contains a compound according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutical carrier.
26. A pharmaceutical composition which contains a compound according to any one of claims 2 to 24, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutical carrier.
27. A method of preparing a medicament for the treatment of diseases of the liver, which comprises the use of a compound according to claim 1.
28. A method of preparing a medicament for the treatment of diseases of the liver, which comprises the use of a compound according to any one of claims 2 to 24.
29. A process for the preparation of an O-substituted derivative of (-)-cyanidan-3-ol of the formula I



(I)

wherein R is as defined in claim 1, or of a salt thereof, which process comprises cleaving the radical OR₁ to the hydroxy group in a compound of the formula II



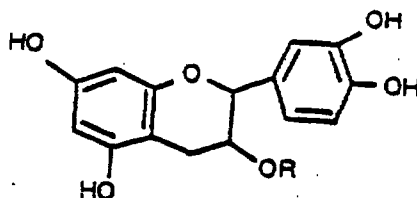
(II)

wherein R₁O is a protected oxy group which is readily hydrolysable or hydrogenatable, and R is as defined above, and, if desired, converting a radical R in a resultant compound by reduction, and/or converting a resultant salt into the free compound or a free compound containing salt-forming groups into the salt.



Revendications (as printed)

1. Nouveaux dérivés O-substitués du (+)-cyanidan-3-ol de formule I



(I)

où R représente:

un radical alcoyle ou alcényle non substitué ou substitué par un hydroxy, un alcanoyloxy inférieur, un alcoyloxy inférieur, un alcanoyloxy inférieur, un cyano, un amino, un mono- ou di-alcoyle inférieur-amino, un alcoylène inférieur-amino, un oxa- ou aza-alcoylène inférieur-amino, un carbamoyle, un mono- ou di-alcoyle inférieur-carbamoyle ou des atomes d'halogène,

un radical cycloalcoyle avant de 3 à 6 atomes de carbone dans son noyau, non substitué ou substitué par un ou plusieurs hydroxy, alcoxy inférieur, alcoyle inférieur, carboxy, oxo, alcanoyloxy inférieur, amino, mono- ou di-alcoyl-amino ou carboalcoyle inférieur,

un radical cycloalcoyl-alcoyle inférieur, qui présente dans son noyau de 3 à 6 atomes de carbone et qui peut être non substitué ou substitué par au moins un radical alcoyle inférieur,

un radical phényle ou naphthyle, qui peut être mono-, di- ou trisubstitué par un hydroxy, un alcoxy inférieur, un carboxy, un carboalcoyle inférieur, un nitro, un amino, un mono- ou di-alcoyle inférieur-amino, ou des atomes d'halogène,

un radical phényl- ou naphthyl-alcoyle inférieur ou -alcényle inférieur qui peut être mono-, di- ou tri-substitué dans son noyau aromatique par un hydroxy, un alcoxy inférieur, un carboxy, un carboalcoyle inférieur, un alcanoyloxy, un nitro, un amino, un mono- ou dialcoyl-amino, un di-alcoyle inférieur-carbamoyle ou des atomes d'halogène (à l'exception du trihydroxy),

un radical aza-, thia-, oxa-, thiaza-, oxaza- ou diaza-cyclique saturé ou insaturé, qui peut être condensé sur un noyau phényle, et qui présente de 2 à 7 atomes de carbone dans le noyau hétérocyclique et qui peut être mono-, di- ou polysubstitué par un alcoyle, un hydroxy, un alcoxy inférieur, un nitro, un carboxy, un carbo-alcoyle inférieur ou un alcanoyloxy,

un radical hétérocyclyl-alcoyle inférieur, dont l'hétérocycle représente un cycle aza, thia, oxa, thiaza, oxaza ou diaza saturé ou insaturé,

un radical d'un acide alcane-carboxylique ayant au moins 3 atomes de carbone, d'un acide alcène inférieur-carboxylique, d'un acide alcane inférieur-dicarboxylique, ou d'un acide alcène inférieur-dicarboxylique,

un radical acide cycloalcane-carboxylique non substitué ou substitué par un ou plusieurs hydroxy, alcoyloxy inférieur, carboxy, carboalcoyle inférieur, alcoyle inférieur, alcanoyloxy inférieur, oxo ou halogène,

un radical benzoyle ou naphtoyle, qui peut le cas échéant être substitué par un hydroxy, un alcoyle inférieur, un alcanoyloxy, un carboxy, un carboalcoyle inférieur, un nitro, un amino ou un halogène,

un radical phényl- ou naphthyl-alcanoyloxy inférieur, qui peut être dans sa fraction aromatique non substitué ou substitué par un hydroxy, un alcoyle inférieur, un carboxy, un carboalcoyle inférieur, un alcanoyloxy inférieur, un alcanoyloxy inférieur, un nitro, un amino, un mono- ou un di-alcoyle inférieur-amino ou un halogène,

un radical d'un acide aza-, thia-, oxa-, thiaza-, oxaza ou diaza-cyclique, qui peut être saturé ou insaturé, ou encore condensé sur un radical phényle,

un radical alcoxycarbonyle,

un radical phényloxycarbonyle,

un radical carbamoyle, qui le cas échéant peut être mono- ou disubstitué par des radicaux alcoyle inférieur, des radicaux phényle ou benzyle, qui le cas échéant peuvent être substitués dans leur noyau par un hydroxy, un alcoyle inférieur, un alcoyloxy inférieur, ou des atomes d'halogène,

un radical d'un acide alcoyle inférieur-sulfonique, ou d'un acide phénylsulfonique, qui peut être substitué dans son noyau par un alcoyle inférieur, un alcoyloxy inférieur ou des atomes d'halogène, ou

le radical d'un acide phosphorique non substitué ou estérifié par 1 ou 2 radicaux alcoyle inférieur ou 1 ou 2 radicaux phényle, l'expression inférieur désignant un radical ayant jusqu'à 7 atomes de carbone, et leurs sels.



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(103)

2. 3-O-méthyl-(+)-cyanidan-3-ol.
3. 3-O-butyl-(+)-cyanidan-3-ol.
4. 3-O-butvryl-(+)-cyanidan-3-ol.
5. 3-O-(3,3-diméthyl-butanoyl)-(+)-cyanidan-3-ol.
6. 3-O-(3-carboxy-propionyl)-(+)-cyanidan-3-ol.
7. 3-O-décanoyl-(+)-cyanidan-3-ol.
8. 3-O-dodécyl-(+)-cyanidan-3-ol.
9. 3-O-heptyl-(+)-cyanidan-3-ol.
10. 3-O-octadécyl-(+)-cyanidan-3-ol.
11. 3-O-palmitoyl-(+)-cyanidan-3-ol.
12. 3-O-(2-carboxy-cyclohexan-carbonyl)-(+)-cyanidan-3-ol.
13. 3-O-benzoyl-(+)-cyanidan-3-ol.
14. 3-O-(4-fluoro-benzoyl)-(+)-cyanidan-3-ol.
15. 3-O-protocatéchyl-(+)-cyanidan-3-ol.
16. 3-O-acétylsalicylyl-(+)-cyanidan-3-ol.
17. 3-O-(2-carboxy-benzoyl)-(+)-cyanidan-3-ol.
18. 3-O-(N-phénylcarbamoyl)-(+)-cyanidan-3-ol.
19. 3-O-méthanesulfonyl-(+)-cyanidan-3-ol.
20. 3-O-(4-méthyl-benzènesulfonyl)-(+)-cyanidan-3-ol.
21. 3-O-(2-cyano-éthyl)-(+)-cyanidan-3-ol.
22. 3-O-(3-amino-propyl)-(+)-cyanidan-3-ol.
23. 3-O-méthoxyméthyl-(+)-cyanidan-3-ol.
24. 3-O-éthoxycarbonyl-(+)-cyanidan-3-ol.

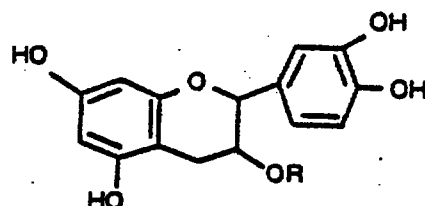
25. Compositions pharmaceutiques caractérisées en ce qu'elles contiennent un composé selon la revendication 1 ou un de ses sels pharmaceutiquement acceptables et au moins un support pharmaceutique.

26. Compositions pharmaceutiques caractérisées en ce qu'elles contiennent un composé selon l'une des revendications 2—24 ou un de ses sels pharmaceutiquement acceptables, et au moins un support pharmaceutique.

27. Application d'un composé selon la revendication 1 comme substance active pour préparer un médicament pour le traitement des maladies hépatiques.

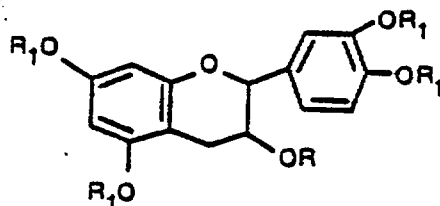
28. Application d'un composé selon l'une des revendications 2—24 comme substance active pour préparer un médicament pour le traitement des maladies hépatiques.

29. Procédé de préparation de dérivés O-substitués du (+)-cyanidan-3-ol de formule I



(I)

où R a la signification donnée dans la revendication 1, et de leurs sels, caractérisé en ce que dans un composé de formule II



(II)

où R.O représente un groupe oxy protégé, qui est facilement hydrolysable ou hydrogénolysable, et R a la signification donnée ci-dessus, on clive la radical OR₁ pour donner un groupe hydroxy et si on le désire, dans un composé obtenu on transforme un radical R par réduction, et/ou en ce que on transforme un sel obtenu en le composé libre ou un composé libre ayant des groupes salificateurs en le sel.