

1.156.769



PATENT SPECIFICATION

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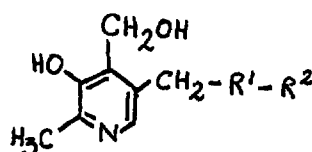
COMPLETE SPECIFICATION

Sulphur-Containing Pyridine Derivatives

We, E. MERCK AKTIENGESELLSCHAFT, of 250, Frankfurter Strasse, Darmstadt, Germany, a Joint-Stock Company organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new sulphur-containing pyridine derivatives and with the preparation thereof.

The new sulphur-containing derivatives of pyridine according to the present invention are compounds of the general formula:—



(I)

wherein

R¹ is a sulphur atom or an —SO-group;

R² is an acyl radical containing up to 4 carbon atoms, —CO.N<^{R³}_{R⁴},

an unsaturated aliphatic hydrocarbon radical containing up to 4 carbon atoms or an alkyl radical which may be substituted by at least one member selected from halogen atoms, hydroxyl and mercapto groups, alkoxy radicals containing up to 4 carbon atoms, alkylthio radicals containing up to 4 carbon atoms and free and functionally changed

carboxy and/or —N<^{R³}_{R⁴} groups, with the proviso that R² signifies a substituent other

than ethyl, β-chloroethyl or β-hydroxyethyl when R¹ is a sulphur atom;

R³ and R⁴, which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 4 carbon atoms or together form a 5- or 6-membered alkylene chain which can be interrupted by at least one member selected from nitrogen, oxygen and sulphur atoms; and the salts of these compounds.

The compounds (I) and the salts thereof are pharmacologically active. As has been shown in animal experiments they increase, in particular, the resistance to oxygen deficiency.

Appropriate experiments have been carried out on rats. The experimental animals were, for this test, subjected to a reduced pressure which corresponded to the reduced atmospheric pressure at a height of, for example, 12000 metres. Subsequently, the electroencephalogram of the experimental animals was recorded via 3 leads attached to the cranium. After the intraperitoneal administration of 100 mg. of an active compound of the above-given general formula (I), for example, of 2-

[Price 4s. 6d.]

methyl-3-hydroxy-4-hydroxymethyl-5-methylthio-methyl-pyridine, in an acute experiment or of 100 mg. amounts of the active compound on 7 successive days in a chronic experiment, the reduced pressure stressing and subsequent recording of the electroencephalogram was repeated.

5 The animals treated in this manner with, for example, 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethylpyridine, showed a clear improvement of resistance to a deficiency of oxygen. It is especially noteworthy that, in these experiments, the effect occurred immediately, whereas in a comparative experiment with the same dosages of the known, chemically closely related compound bis-[2-methyl-3-hydroxy-4-hydroxymethyl-pyridyl-(5)-methyl]-disulphide, which can be used for the same indication, such an immediate effect is not achieved.

Some of the compounds of the above-given general formula (I) also show a physiologically protective action against the harmful influences of energy-rich radiations.

15 Furthermore, the new compounds according to the present invention, in comparison with the above-mentioned, previously known bis-[2-methyl-3-hydroxy-4-hydroxymethylpyridyl-(5)-methyl]-disulphide, are characterised in that their water- and lipid-solubility can be varied by variation of the substituent R^2 with regard to the length of the chain and the nature of the substituents therein.

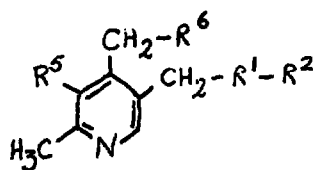
20 Thus, for example, 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethylpyridine according to the present invention is 10 times more soluble in water than the previously known disulphide used in the above-mentioned experiment and 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylsulphinylmethyl-pyridine, which is also according to the present invention, is 100 times more water-soluble than this known compound.

25 Compounds of the above-given general formula (I) which are substituted in the radical R^2 by amino and/or carboxy groups also have the advantage that they are water-soluble in the physiological pH range and are, therefore, especially suitable for the production of injection solutions. In contradistinction hereto, the above-mentioned, previously known disulphide is not soluble in water in the physiological pH range.

30 Compounds of the above-given general formula (I) which contain comparatively long alkyl radicals in R^2 are characterised, in comparison with the previously known bis-[2-methyl-3-hydroxy-4-hydroxymethyl-pyridyl-(5)-methyl]-disulphide, by an increased lipid solubility. These compounds penetrate the cell membranes comparatively quickly and are better taken up by the lipid-rich nervous tissues.

35 The present invention is also concerned with a process for the preparation of the above-mentioned new compounds of general formula (I) and of the salts thereof. Thus, for example, the new compounds can be prepared in that:

a) in a starting material of the general formula: —



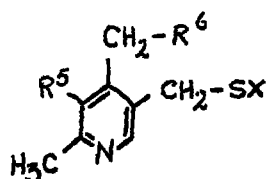
(II)

40 wherein

R^5 and R^6 , which may be the same or different, are free or functionally changed hydroxyl groups; and

45 R^1 and R^2 have the above given meanings and whereby the radical R^2 can contain at least one hydroxyl and/or amino group which has been undesirably functionally changed, with the proviso that at least one of the radicals R^5 and R^6 is a functionally changed hydroxyl group, or a salt thereof, the functionally changed hydroxyl groups and the functionally changed amino groups, when present, are converted into free groups; or

b) a 5-thiomethyl-pyridine derivative of the general formula: —

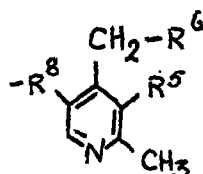


(III)

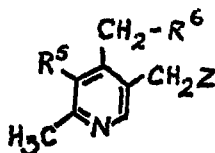
wherein

R^5 and R^6 , which may be the same or different, are free or functionally changed hydroxyl groups; and

- 5 X is a hydrogen atom or an alkali metal or alkaline earth metal cation, preferably a sodium ion, or is an unsubstituted or substituted undesired alkyl, aryl or aralkyl radical or is an unsaturated aliphatic hydrocarbon radical or an undesired acyl radical or a radical of the general formula: —



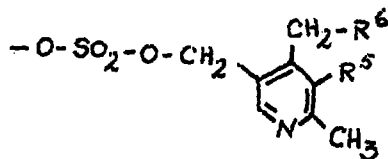
- 10 wherein R^8 is a methylene radical or a thiaethylene radical, or a salt thereof is reacted with an alkylation or acylation agent; or
- c) a pyridine derivative of the general formula: —



(IV)

wherein

- 15 Z is a sulphonic acid residue, especially a *p*-toluene-sulphonyloxy radical, or a halogen atom, especially a chlorine or bromine atom, or a radical of the general formula: —



wherein

- 20 R^5 and R^6 have the same meanings as in general formula (III), or a salt thereof is reacted with a mercapto compound of the general formula: —



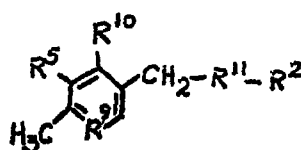
(V)

wherein

- 25 Y is a hydrogen atom or an alkali metal or alkaline earth metal cation, preferably a sodium ion; and

R^2 has the same meaning as above; or

d) a pyridine derivative of the general formula: —



(VI)

wherein

R^9 is N or $\text{N}=\text{O}$

R^{10} is a $-\text{CH}_2\text{R}^5$ group or a free or functionally changed formyl group, and

R^{11} signifies an $-\text{S}-$, $-\text{SO}-$ or $-\text{SO}_2-$ group with the proviso that R^9 is

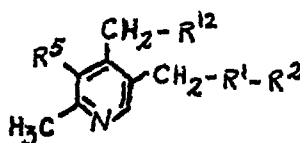
always $\text{N}=\text{O}$ when R^{10} is $-\text{CH}_2\text{R}^5$ and R^{11} is $-\text{S}-$ and that R^{10} is always free or

functionally changed formyl group when R^9 is N and R^{11} is $-\text{S}-$ and that R^{11} is $-\text{S}-$ and that R^{11} is always H

always $-\text{SO}-$ or $-\text{SO}_2-$ when R^9 is N and R^{10} is $-\text{CH}_2\text{R}^5$, and wherein

R^2 , R^5 and R^6 have the same meanings as in general formulae (I) and (III), whereby, in addition, the radical R^2 can also contain undesired substituents which can be split off by reduction or can be converted into desirable substituents as given above in the definition of R^2 , or a salt thereof, is treated with a reducing agent and, if necessary, also with a nucleophilic reagent, especially with a base; or

e) in a pyridoxamine derivative of the general formula: —



(VII)

wherein

R^{12} is an amino group, which can be substituted by acyl radicals or by a tri-phenyl-methyl radical, and

R^1 , R^2 and R^5 have the same meanings as in general formulae (I) and (III), or a salt thereof, the amino group R^{12} is converted into a hydroxyl group by treatment with nitrous acid; or

f) a 5-thiomethyl-pyridine derivative of the above-given general formula (III), wherein X is a hydrogen atom or an alkali metal or alkaline earth metal cation, is added to an alkene or alkyne, which can be substituted by at least one member selected from halogen, hydroxyl, C_1-C_4 alkoxy, mercapto, C_1-C_4 alkylthio and

optionally functionally changed carboxy and/or $-\text{N} < \begin{smallmatrix} \text{R}^3 \\ \text{R}^4 \end{smallmatrix}$; or

g) in a compound of the above-given general formula (I) or in a salt thereof which, however, contains in the radical R^2 undesired substituents, especially halogen, $=\text{CO}$, NO_2 , NO and/or $-\text{COOH}$ and/or carbon-carbon multiple bonds or still does not contain desired substituents, especially NH_2 , $\text{N}(\text{CH}_3)_2$, COOH , SH and/or OH and/or desired carbon-carbon multiple bonds, the undesired substituents are split off or converted into desired substituents and/or the undesired carbon-carbon multiple bonds are hydrogenated or the desired substituents and/or carbon-carbon multiple bonds are introduced.

Furthermore, according to the present invention protective groups still present in the radicals R^5 and R^6 after carrying out reactions (b) to (g) can be split off under the conditions of reaction (a).

If desired, the compounds obtained of the above-given general formula (I) in which R^1 is $-\text{S}-$ can also be oxidised to the corresponding compounds in which R^1 is an $-\text{SO}-$ group.

The free bases of the above-given general formula (I) obtained according to

the present invention can also be converted into their acid-addition salts or into their quaternary ammonium salts or into their tertiary sulphonium salts or can be liberated from their acid-addition salts or from their quaternary ammonium salts or from their tertiary sulphonium salts.

The present invention is also concerned with pharmaceutical preparations which contain an effective dose of a compound of the above-given general formula (I) or of a salt thereof, together with the conventional pharmaceutical carriers and adjuvants.

In the compounds (I) according to the present invention, the substituent R^1 signifies —S— or —SO—, those compounds in which R^1 is —S— being preferred.

The radical R^2 in the compounds (I) can have the following meanings: C_1 — C_4 acyl, for example, acetyl, propionyl, butyryl, the acetyl radical being preferred; or —CONR³R⁴, wherein R^3 and R^4 , which may be the same or different, can signify hydrogen atoms or substituents as hereinafter defined.

Furthermore, the radical R^2 can signify an unsaturated aliphatic hydrocarbon radical containing up to 4 carbon atoms, preferably an alkenyl radical, such as vinyl, allyl, propenyl or butenyl radical, or an alkynyl radical, such as an ethynyl or propargyl radical.

Those compounds of general formula (I) in which R^2 is an alkyl radical, which may be substituted in the manner described in general formula (I), are especially important. The alkyl radical can be straight chained or branched and, in general, does not contain more than 20 carbon atoms. Examples of alkyl radicals include, apart from the longer alkyl radicals, such as hexyl, heptyl, octyl and dodecyl radicals, in particular the alkyl radicals containing up to 4 carbon atoms, such as methyl, *n*-propyl, isopropyl, *n*-butyl and isobutyl radicals. Those compounds in which the substituent R^2 is a methyl radical are especially preferred.

The alkyl radical R^2 can be substituted one or more times.

In the case of substitution by halogen atoms, chlorine and bromine atoms are the preferable substituents.

Further substituents which may be present in the alkyl radical R^2 are, apart from hydroxyl groups, also alkoxy radicals containing up to 4 carbon atoms, such as methoxy and/or ethoxy radicals.

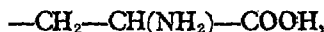
Furthermore, mercapto groups or also alkylthio groups containing up to 4 carbon atoms, especially methylthio groups, can be present in an alkyl radical R^2 .

As substituents in R^2 , there can also be present amino groups —NR³R⁴, whereby R^3 and R^4 , which may be the same or different, can signify hydrogen atoms or alkyl radicals containing up to 4 carbon atoms or R^3 and R^4 can together form an alkylene radical, which may be interrupted by at least one member selected from nitrogen, oxygen and sulphur atoms. Together with the nitrogen atom of the amino group to which they are attached, R^3 and R^4 can thus form, for example, a piperidino, morpholino, piperazino or thiomorpholino radical. The substituents R^3 and R^4 are preferably the same and preferably signify hydrogen atoms or methyl or ethyl radicals. As examples of amino-substituted alkyl radicals R^2 there may be mentioned the following: 2-aminoethyl, 2-aminopropyl, 3-amino-2-methyl-propyl and 4-aminobutyl radicals, as well as the corresponding N-methyl, N-ethyl-, N-propyl, N-butyl, N,N-dimethyl, N,N-diethyl-, N-methyl-N-ethyl- and piperidino derivatives. However, the 2-aminoethyl radical is particularly preferred, as well as the corresponding N-mono- and N,N-di-methyl and -ethyl derivatives thereof.

The alkyl radical R^2 can also be substituted by a free carboxyl group or by a functionally changed carboxyl group, especially by an esterified or amidated carboxyl group containing a total of up to 8 carbon atoms. As esterified carboxyl groups, there can be mentioned, for example, the carbalkoxy groups containing up to 4 carbon atoms, such as the carbomethoxy or carboethoxy radicals, as well as the carbobenzoxy radical. As amidated carboxyl group, the —CONH₂ is particularly preferred. However, the hydrogen atoms of the amino group can also be replaced by alkyl radicals containing up to 4 carbon atoms which can also be joined together to form an alkylene radical, which can be interrupted by hetero atoms such as nitrogen, oxygen and/or sulphur atoms. Thus, besides the radical —CONH₂, there can also be used, for example, the N-methyl-, N-ethyl-, N-butyl-, N,N-dimethyl-, N, N-diethyl, N,N-di-propyl- or N-methyl-N-ethyl-amide groups, as well as the piperidides, piperazides, morpholides or thiomorpholides, the preferred radicals being those in which the amidated carboxyl group is —CONR³R⁴, in which R^3 and R^4 are the same and signify hydrogen atoms or methyl or ethyl radicals. The preferred substituents in the

radicals R^2 are $-\text{COOH}$, $-\text{COOC}_2\text{H}_5$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_3)_2$ and $-\text{CON}(\text{C}_2\text{H}_5)_2$.

It is also possible for the alkyl radical R^2 to contain different substituents, for example, amino and carboxyl groups, at the same time. Thus, for example, R^2 can signify an ω -amino- ω -carboxy-alkyl radical, such as the radical



and including related radicals in which the carboxyl group is replaced by an ester or amide group or is functionally changed in some other manner.

Preferred compounds of the above-given general formula (I) are those in which R^2 has the following meanings: $-\text{COCH}_3$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{CON}(\text{C}_2\text{H}_5)_2$, vinyl or propargyl or an alkyl radical containing up to 4 carbon atoms which can be substituted by chlorine, bromine, $-\text{NR}^3\text{R}^4$, hydroxyl, mercapto, methyl-mercapto and/or carboxyl, which latter can be free or esterified or can be converted into an amide group.

Amongst the preferred compounds (I) in which R^1 is a sulphur atom, there can, by way of example, be mentioned the following: 2-methyl-3-hydroxy-4-hydroxymethyl-5-(methylthiomethyl)-pyridine; 2-methyl-3-hydroxy-4-hydroxymethyl-5-(dimethylcarbamoyl - thiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (vinylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (propargylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (isopropylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (n - butylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (hydroxymethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - mercaptoethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (methylthioethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (carbethoxymethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - aminoethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - dimethylaminoethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - amino- β -carboxyethylthiomethyl)-pyridine.

There may also be mentioned the following compounds in which the substituent is an $-\text{SO}-$ group: 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (methylsulphinylmethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (ethylsulphinylmethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (vinylsulphinylmethyl) - pyridine; and 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (propargylsulphinylmethyl)-pyridine.

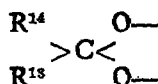
Besides the free bases of the above-given general formula (I), the present invention also includes their salts, i.e. the acid-addition salts, especially those with strong mineral acids, such as the hydrohalic acids, for example, hydrochloric acid and hydrobromic acid, as well as sulphuric acid, and the quaternary ammonium salts, as well as the tertiary sulphonium salts.

Particularly important is the pharmacologically very effective compound 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine and the acid addition salts thereof, for example, its hydrohalides, especially the hydrochloride, and also the sulphate thereof. Amongst the quaternary ammonium and tertiary sulphonium salts of this compound, the methiodide is to be particularly mentioned.

In the following, the processes for the preparation of the new compounds according to the present invention are described by way of preferred embodiments:

a) According to the present invention, compounds (I) can be obtained in that, in a starting material of the above-given general formula (II) which contains, in the 3- and/or 4'-position, functionally changed hydroxyl groups, these hydroxyl groups are liberated.

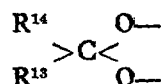
As starting materials for this process, there are preferably used compounds of the above-given general formula (II) in which R^5 and/or R^6 signify acyloxy radicals, especially acyloxy radicals containing up to 4 carbon atoms, such as acetoxy, propoxy or butoxy radicals, the acetoxy radical being preferred, or together signify the group-



wherein R^{13} and R^{14} , which may be the same or different, signify hydrogen atoms or alkyl radicals containing up to 4 carbon atoms or together with the carbon atom to which they are attached represent cycloalkylidene or aralkylidene radicals which preferably contain up to 7 carbon atoms, and a $=R^{13}R^{14}$ fragment is, for example, methylene, ethylidene, isopropylidene, cyclohexylidene or benzylidene radicals. Furthermore, the substituents R^5 and R^6 can also signify alkoxy radicals, especially alkoxy radicals containing up to 4 carbon atoms, such as methoxy, ethoxy or *n*-propoxy radicals.

For the liberation of the hydroxyl group or groups, saponifying acidic or alkaline reagents are preferably used.

The hydroxyl groups are preferably liberated in the substituents R^5 and/or R^6 by means of acidic agents. Thus, for example, acidic agents are used when an alkylidene radical is to be split off from the substituents R^5 and R^6 . In the case of acidic hydrolysis, hydroxyl groups can be liberated in the substituents R^5 and R^6 with, for example, mineral acids, especially with hydrochloric acid, hydrobromic acid or sulphuric acid. Furthermore, for the acidic splitting off there can also be used, for example, hydrobromic acid/acetic acid, pyridine hydrochloride (which may be accomplished therewith at an elevated temperature) or Lewis acids, especially boron trifluoride or aluminium trichloride, in appropriate solvents, such as ether or tetrahydrofuran. The splitting off of the acyl groups takes place, for example, efficiently by the action for about half an hour of hydrochloric acid at boiling temperature. Starting materials (II) in which the substituents R^5 and R^6 together represent the grouping:—

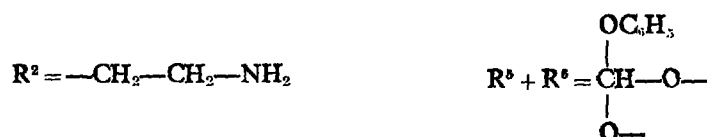
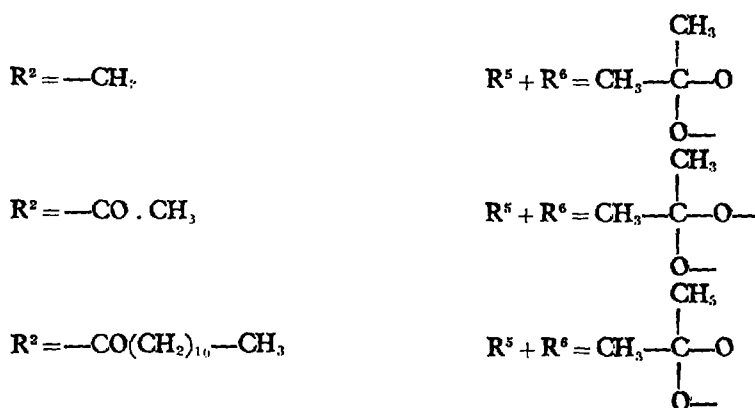


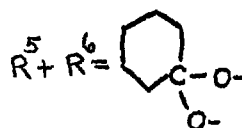
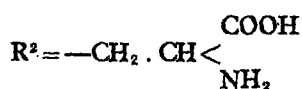
can even be liberated with very dilute acids, for example with 0.01N sulphuric acid.

Insofar as starting materials of general formula (II) are used in which R^5 and/or R^6 are acylated hydroxyl groups (for example $R^5 = R^6 = -O \cdot CO \cdot CH_3$, $-O \cdot CO \cdot C_2H_5$, $-O \cdot CO \cdot C_3H_7$ or benzoyloxy), the protective groups can also be split off under alkaline conditions, for example, with the use of alkali metal hydroxides or carbonates, such as sodium or potassium carbonate.

In the case of this method, functionally changed hydroxyl and/or amino and/or carboxyl groups in the R_2 side chain can also be liberated.

Preferred starting materials for this method are, for example, compounds of the above-given general formula (II) in which R^1 is a sulphur atom and





These starting compounds can be obtained, for example, by the alkylation or acylation of a compound of general formula (II) in which, however, there is a hydrogen atom or sodium ion instead of R^2 , with a compound of the general formula $R^2 \cdot \text{Hal}$ or with an acyl halide, followed, if desired, by oxidation of the radical $R^1 = -S-$ to give the radical $R^1 = -SO-$ by methods known from the literature.

b) For the introduction of the radical R^2 into a starting compound (III) according to the above - mentioned method (b), there can be used the agents normally employed for S-alkylations and S-acylations, for example, the methods described in Houben-Weyl's "Methoden der organischen Chemie", 4th edition, Volume 9 (1955), pub. Georg-Thieme-Verlag, Stuttgart, page 97 *et seq.*

In particular, for the alkylation there can be used appropriate reactive esters which contain the substituent R^2 , especially alkyl halides or sulphuric acid esters or sulphonic acid esters, especially the *p*-toluene-sulphonic acid esters. For example, there can be used appropriate, unsubstituted or substituted alkyl chlorides, bromides, iodides or sulphates of the general formula $R^2 \cdot \text{Hal}$ or $(R^2)_2\text{SO}_4$, respectively, wherein R^2 has the above-given meaning, for example, methyl iodide, propyl chloride, butyl bromide, β -chloroethylamine; α -amino- β -chloropropionic acid; β -chloroethyl mercaptan, dimethyl sulphate, ethyl chloroformate, chloroacetic acid esters, allyl bromide, propargyl chloride, methyl *p*-toluene-sulphonate, propyl bromide or iodide, isopropyl bromide or iodide, *sec*-butyl bromide, *sec*-butyl iodide, diethyl sulphate, ethyl *p*-toluene-sulphonate, β -hydroxyethyl *p*-toluene-sulphonate, β -chloroethyl *p*-toluene-sulphonate, chloroacetic acid, bromoacetic acid, β -piperidino-ethyl chloride and bromide, *N*-(β -chloro- or -bromo-ethyl)-morpholine, *N*-(β -chloro- or -bromoethyl)-thio-morpholine.

For the introduction of the aminoethyl radical, ethylene-imine can be used as alkylation agent.

Examples of starting materials (III) include [3-hydroxy-4-hydroxymethyl-2-methyl-pyridyl-(5)]-methyl mercaptan and [3-acetoxy-4-acetoxymethyl-2-methyl-pyridyl-(5)]-methyl mercaptan and the corresponding mercaptides, especially the sodium mercaptides. The starting materials (III) can be obtained, for example, by the reaction of the corresponding 5-halomethyl-pyridine compounds with alkali metal hydrogen sulphides, thiourea or potassium thiocarbonate, followed, if desired, by reaction with alkali.

The alkylation of the starting materials (III) is expediently carried out by mixing together the reaction components in an inert solvent, if necessary with cooling. For example, a mercaptide (III) is dissolved in an aqueous or alcoholic solution and the alkylation agent, for example, an alkyl halide or a dialkyl sulphate, is added either in an equivalent amount or in slight excess. The reaction can be carried out at ambient temperature, for example by leaving the reaction mixture to stand overnight. It is also possible to work at an elevated temperature, for example, the alkylation can be carried out by heating the reaction mixture for a few hours on a steambath.

Insofar as starting materials (III) are used in which the radicals R^5 and R^6 signify free hydroxyl groups, it is recommended not to use the alkylated agent in excess in order to avoid undesirable O-alkylation. After completion of the reaction, the reaction mixture can, if necessary, be neutralised. In general, the desired end product precipitates out of the solution upon cooling.

Furthermore, it is also possible to alkylate in the usual manner, for example, a mercaptan (III) in water or in an alcohol in the presence of an alkali metal or alkaline earth metal compound, for example, an alkali metal or alkaline earth metal hydroxide or an alkali metal alcoholate, such as sodium methylate or ethylate, a mercaptide of general formula (III) (X =an alkali metal or alkaline earth metal cation) initially being formed. After completion of the reaction, in the case of alkylation in an alcohol, the solvent is expediently removed by evaporation of the reaction mixture. Subsequently, the salts contained in the mixture can be removed by treatment with water and from the residue the end product formed can be isolated by extraction with an appropriate organic solvent, for example, ethyl acetate or a chlorinated hydrocarbon, such as chloroform, methylene chloride or trichloroethylene, or

with an ether, followed by evaporation of the extraction agent.

By the reaction with an alkylation agent under the above-described conditions, it is also possible to exchange an undesired substituent X in the starting material (III) for a desired alkyl radical. By the reaction of a starting material (III), which contains an undesired substituent X as defined above, with, for example, a methyl halide, especially methyl iodide, there is obtained, for example, a compound of the above-given general formula (I) in which R² is a methyl radical. It is also possible to use salts, for example, sulphonium salts of the starting materials (III) for this alkylating fission.

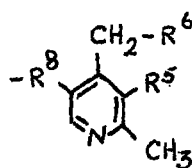
If, in this method, there are used starting materials (III) in which X signifies an unsubstituted or substituted, undesired alkyl radical or also an aryl or aralkyl radical, which may be substituted, then the desired radical R² is introduced by reaction with an alkylation agent under the above-described conditions by means of transalkylation. Examples of starting materials for this special variant of method (b) according to the present invention are, for example, compounds of the above-given general formula (III) which contain, as substituent X, —CO . CH₂ . C₆H₅ or —CH₂—CH=CH₂, which can be trans-alkylated with, for example, methyl iodide, to give a compound (I) in which R¹ is a sulphur atom and R² is a methyl radical. In the same way, in starting compounds (III) which contain a methyl radical as the substituent X, this radical can be replaced, for example, by transalkylation with, for example, chloroacetic acid to give a product in which R² is —CH₂ . COOH. As starting materials, there can be used, for example, the following compounds; 2-methyl-3-hydroxy-4-hydroxymethyl-5-phenacylthiomethyl-pyridine, 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5-benzylthiomethyl-pyridine and 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine.

The more detailed conditions for the carrying out of the transalkylations or transacylations are described in Houben-Weyl, *ed. cit.*, Volume 9 (1955), page 190; Chem. Ber., 83, 90(1950) and 86, 1049 (1953); and in Am. Chem., 566, 139(1950).

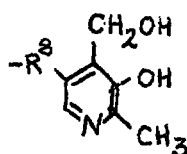
The starting materials can be obtained, for example, by the alkylation of a compound of the above-given general formula (III) under the conditions described above under (b).

In the compounds (III), by treatment with, for example, an alkyl halide, especially with a methyl halide, such as methyl bromide or methyl iodide, the undesired radical X is removed, with the simultaneous introduction of the desired substituent R².

Insofar as starting materials of the above-given general formula (III) are used in which the substituent X is a grouping of the general formula: —



wherein R⁵, R⁶ and R⁸ have the above-given meanings, there is obtained, in the case of this reaction according to the present invention, by reaction with an alkylation agent, the desired end product of the above-given general formula (I) by alkylating fission. In the case of this alkylating fission, in end effect the undesired substituent X is also replaced by the desired substituent R². As starting materials for this variant of method (b) of the present invention, there can be used S-alkyl compounds, for example, an S-methyl compound or bis-[2-methyl-3-hydroxy-4-hydroxymethyl-pyridyl-(5)-methyl]-di- (or -mono-) sulphide, i.e. above-given general formula (III) in which R⁵ and R⁶ are hydroxyl groups and X is a radical of the general formula: —



These starting materials can be obtained, for example, by the reaction of a compound of general formula (III) (X is a sodium ion) with a compound of general

formula (IV) (Z is a halogen atom) or of a compound of general formula (IV) (Z is a halogen atom) with an alkali metal disulphide, for example sodium disulphide.

Furthermore, compounds of general formula (I), which contain $-\text{CH}_2\text{OH}$ as the substituent R^2 , can be prepared from the starting materials (III), in which X is a hydrogen atom, by reaction with formaldehyde. Expediently, for this purpose, a mercaptan or mercaptide (III) in aqueous solution, to which an inert organic solvent, especially alcohol, has possibly been added, is reacted with an aqueous, preferably 40%, solution of formaldehyde and left to stand for some hours, for example overnight. In this case, it is advantageous to use an excess of formaldehyde.

For the introduction of a methyl radical as substituent R^2 into a starting material (III), in which X is a hydrogen atom and R^3 and R^6 have the above-given meanings, there can also be used, in particular, diazomethane as the alkylation agent. In this case, the reaction is carried out, for example, under the conditions described in "Neuere Methoden der preparativen organischen Chemie", published by W. Foerst, Verlag Chemie, Weinheim (1949), 3rd edition, Volume I, pages 359—412.

A substituent $\text{R}^2 = \text{acyl}$ or $-\text{CONR}^3\text{R}^4$ can be introduced into a starting material of general formula (III) (X = a hydrogen atom or an alkali metal or alkaline earth metal cation or an undesired acyl radical) by treatment with conventional acylation agents or with an N-mono- or disubstituted carbamic acid halide.

For the acylation of the starting materials (III), there can be used carboxylic acids or the reactive derivatives thereof which are usually employed for esterifications, especially acid chlorides, acid anhydrides, especially symmetrical acid anhydrides, as well as ketenes. For the introduction of the substituents $-\text{CONR}^3\text{R}^4$, the starting material (III) is treated with carbamyl chlorides, such as carbamyl chloride *per se*, or substituted carbamyl chlorides, for example, carbamyl chlorides substituted by lower alkyl radicals, such as dimethyl- or diethyl-carbamyl chlorides. The conditions for this special method of preparation are described, for example, in Houben-Weyl's "Methoden der organischen Chemie", 4th edition, Thieme-Verlag, Stuttgart, Volume 9 (1955), pages 753—756. By the reaction of a starting material of general formula (III) (X = H or Na) with, for example, an acetyl halide, especially acetyl chloride or bromide, or with acetic anhydride or with ketene, the acetyl radical can be introduced on to the sulphur atom. Furthermore, an acyl radical R^2 can be introduced in a starting material (III) (X is hydrogen) by reacting a carboxylic acid with the starting material in the presence of a carbodiimide, especially of dicyclohexyl carbodiimide. There are preferably used inert solvents which contain no active hydrogen atoms, such as halogenated hydrocarbons, for example, chloroform or methylene chloride, or nitrohydrocarbons, such as nitromethane, or acetonitrile or ethyl acetate.

Furthermore, compounds of the above-given general formula (I), in which R^2 is an acyl radical, can be reacted to give the corresponding iminothioether hydrochloride by reaction of the starting materials (III) (X is hydrogen) with a nitrile and hydrochloric acid or to give the corresponding thiourethane-S-ester by reaction with an isocyanate. The intermediate products thus obtained are then hydrolysed subsequently to give the desired compounds of general formula (I), in which R^2 is an acyl radical. In this case, the reaction is carried out, for example, under the conditions described in Houben-Weyl's "Methoden der organischen Chemie", 4th edition, Volume 9, page 763 *et seq.* or page 831 *et seq.* or page 819 *et seq.* (1955). The hydrolysis of the iminothioether hydrochlorides is carried out, for example, with hydrochloric acid/water.

The acylation is expediently carried out under mild conditions when R^5 and R^6 in the starting materials (III) are free hydroxyl groups. When R^5 and R^6 are functionally changed hydroxyl groups in the starting materials, it is also possible to work under more vigorous conditions. In the case of this method of carrying out the reaction, the hydroxyl groups in the starting materials are preferably protected.

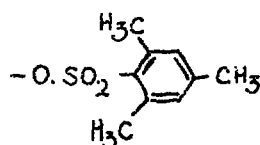
Starting materials (III), in which X is an undesired acyl radical, are converted into the desired end products of the above-given general formula (III) by the mentioned acylation agents by means of transacylation.

In the case of the alkylations and acylations, there can be used, as starting materials, besides the basic compounds of the above-given general formula (III), also their salts, especially their quaternary ammonium salts and/or possibly their sulphonium salts and, in particular, their acid-addition salts.

c) According to the present invention, there can also be used, as starting materials, the pyridine compounds of the above-given general formula (IV). In these compounds,

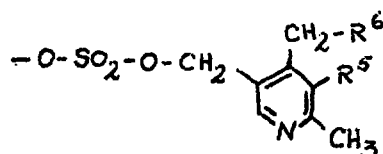
the substituent R^2 is introduced by reaction with a mercapto compound of the above-given general formula (V) under substantially the same conditions as have been described above for the alkylation and acylation of the starting materials (III).

In the starting materials (IV) Z signifies a halogen atom, preferably a bromine or chlorine atom, or a sulphonic acid residue, especially $-\text{O} \cdot \text{SO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_3$,
 $-\text{O}-\text{SO}_2 \cdot \text{C}_6\text{H}_4\text{Br}$, $-\text{O} \cdot \text{SO}_2 \cdot \text{C}_6\text{H}_5$,



or $-\text{O} \cdot \text{SO}_2 \cdot \text{CH}_3$,

the *p*-toluene-sulphonic acid residue being preferred, or the radical of a sulphuric acid ester of the general formula: —



especially preferred starting materials are those in which the substituent Z is a halogen atom, particularly a bromine or chlorine atom.

Examples of starting materials (IV) include 5-chloromethyl-3-hydroxy-4-hydroxymethyl-2-methyl-pyridine; 5-bromomethyl-3-hydroxy-4-hydroxymethyl-2-methyl-pyridine; 3-acetoxy-4-acetoxymethyl-5-chloro- and -5-bromomethyl-2-methyl-pyridine and 2-methyl-3-hydroxy-4-hydroxymethyl-5-*p*-toluene-sulphonyl-methyl-pyridine and their acid addition salts, especially the hydrochlorides, hydrobromides and sulphates. The starting materials (IV) can be obtained, for example, by the halogenation of pyridoxine with phosgene, thionyl chloride, phosphorus trichloride or hydrogen bromide.

The preparation of compounds of the above-given general formula (I) which contain a C_1-C_4 acyl radical as the substituent R^2 takes place, in this case, by reaction of the starting materials (IV), especially of the corresponding 5-halomethyl derivatives, with a thiocarboxylic acid or with a thiocarbamic acid derivative or with the corresponding alkali metal derivatives (general formula (V) in which R^2 signifies a C_1-C_4 acyl radical or the group $-\text{CONR}^3\text{R}^4$). This reaction can, for example, be carried out according to the conditions described in Houben-Weyl's "Methoden der organischen Chemie", 4th edition, Volume 9 (1955), page 749 *et seq.* The reaction is expediently carried out in an appropriate solvent, for example, an alcohol, especially an aliphatic alcohol containing up to 4 carbon atoms, such as methanol, ethanol, propanol, isopropanol or *n*-butanol, or in dimethyl formamide. The preferred solvent is ethanol. Furthermore, in the case of this method, it is advantageous to work in the presence of an alkali, for example, in an alcoholic solution of potassium hydroxide. In general, the reaction is carried out at ambient temperature. However, sometimes it is also expedient to heat the reaction mixture or even to boil it under reflux.

It is especially advantageous when there is used, for example, an alcoholic solution of potassium hydroxide in slight excess and the thiocarboxylic acid added thereto, the potassium salt of the acid thereby being formed. To the alkaline solution of the thiocarboxylic acid salt there is then added the stoichiometric amount or an excess of the starting compound (IV). The compound (I) obtained is then isolated in the usual manner, for example, by extraction with a suitable solvent, such as ether, and possibly with subsequent recrystallisation.

Insofar as the substituents R^5 and R^6 in the starting materials (IV) represent hydroxyl groups, the thioacylation is expediently carried out under mild conditions. When R^5 and R^6 in the starting material are functionally changed hydroxyl groups, it is possible to work under more severe conditions, for example, even at an elevated temperature.

d) According to the present invention, the compounds (I) can also be prepared by the reduction of starting materials of the above-given general formula (VI) or of the salts of these compounds.

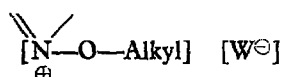
For example, a starting material of the above-given general formula (VI) which

contains the substituents $R^9 = \text{NO}$ and $R^{11} = \text{—SO—}$ or $\text{—SO}_2\text{—}$, can be converted, by treatment with reducing agents, such as zinc/dilute hydrochloric acid or iron/hot acetic acid or phosphorus trichloride or tribromide, into the corresponding compounds of the above-given general formula (I) which no longer contains the pyridine ring in the oxidised form and contains the desired radical $R^1 = \text{S}$. The reduction by warming with ammonium sulphide or by heating with phosphorus trichloride, for example in chloroform, or by treatment with iron powder in hot acetic acid, is preferred. Hydrogenation with the usual catalysts, for example, 5% palladium charcoal or Raney nickel in appropriate solvents, such as ethanol or acetic anhydride, can also be used for the conversion of a starting material of general formula (VI), which

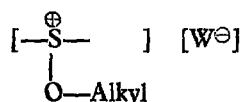
contains the substituents $R^9 = \text{NO}$ and $R^{11} = \text{SO}$ or SO_2 , into an end product (I) which no longer contains the pyridine moiety in the oxidised form and which contains the desired substituent $R^1 = \text{S}$. This reduction is carried out under the conditions known from the literature, for example, in *Archiv Pharm.*, 287, 326 (1954); *J.Org.Chem.*, 18, 534 (1953); *Rec. trav.chim.Pays-Bas*, 70, 581 (1951); *J.Pharm.Soc.Japan*, 71, 1092 (1952); Houben-Weyl's "Methoden der organischen Chemie", 4th edition, Volume 11/12, page 200 *et seq.*, pub. Georg-Thieme-Verlag, Stuttgart.

Besides the basic compounds of the above-given general formula (VI), the salts of these compounds can also be used as starting materials for the carrying out of method (d).

This, for example, salts corresponding to general formula (VI) which contain



instead of R^9 and



instead of R^{11} (Alkyl hereby signifies an unsubstituted or substituted alkyl radical and W^- signifies an equivalent of an anion, such as Cl^- , Br^- , I^- or $\frac{1}{2}\text{SO}_4^{--}$) can also be converted, by reduction, into the desired compounds (I) in which $R^1 = \text{—S—}$. For this purpose, there are used the processes known for the reduction of amine-alkoxides to amines or of O-alkylated sulfoxides to thioethers, for example, non-noble metals, such as zinc, with acids or complex metal hydrides, such as sodium borohydride in ethanol or tetrahydrofuran. Furthermore, salts of these compounds (VI) ($R^{10} = \text{—CH}_2\text{R}^6$) can also be converted, by treatment with nucleophilic reagents, preferably with bases, such as aqueous alkali metal hydroxides or silver oxides, into the desired compounds of the above-given general formula (I), in which $R^1 = \text{—S—}$. The conditions under which the special form of the process is carried out are, for example, described in *J.Pharm.Soc. Japan*, 64, 210 (1944); *J.Org.Chem.*, 18, 534 (1953); *J.Org.Chem.*, 32, 1926 (1967); *J.Org.Chem.*, 32, 3233 (1967).

Furthermore, in method (d) according to the present invention, starting materials (VI) which, as substituent R^{10} on the pyridine ring, contain a free or functionally changed formyl group, can be converted into the desired end products (I) by reduction according to the processes known for the conversion of formyl groups into hydroxymethyl groups. Preferred starting materials for this method are compounds of general formula (VI) in which $R^{10} = \text{CHO}$. For example, the following compounds (VI) can be used as starting materials: 2-methyl-3-hydroxy-4-formyl-5-methylthiomethylpyridine; 2-methyl-3-hydroxy-4-formyl-5-carbethoxymethylthiomethylpyridine; 2-methyl-3-hydroxy-4-formyl-5-aminoethylthiomethylpyridine; and 2-methyl-3-hydroxy-4-formyl-5-dimethylaminoethylthiomethylpyridine. Examples of reducing agents which can be used include complex metal hydrides, especially lithium aluminium hydride or sodium borohydride, non-noble metals and acids, especially zinc or iron/acetic acid, aluminium amalgam/water and aluminium isopropylate/isopropanol, as well as catalytically activated hydrogen. The more detailed

conditions under which it is hereby possible to work are described, for example, in Weygand-Hilgetag, *ed.cit.*, pages 154—169.

As functionally changed formyl groups R^{10} in the starting materials (VI), there are preferably used acetals with alcohols containing up to 4 carbon atoms and also with araliphatic alcohols, such as benzyl alcohol. The conditions for the preparation of these pyridoxal-acetals (compounds (VI) in which R^{10} is, for example $-\text{CH}(\text{OC}_2\text{H}_5)_2$) are, for example, described in detail in Houben-Weyl, *ed.cit.*, Volume 6/3 (1965), pages 199—270. In the pyridoxal-acetals, the hydroxyl group in the 5'-position can be replaced, in the manner known from the literature, by halogen and this in turn by $-\text{SH}$ or R^3R^2 .

The fission of these acetals, with the simultaneous reduction of the 4'-carbonyl group to a 4'-hydroxyl group, takes place, in particular, with the use of catalytically activated hydrogen under the conditions which are described in more detail in Houben-Weyl, *ed.cit.*, volume 6/3 (1965), pages 277—278.

Insofar as reducible substituents are present in R^2 in the starting material (VI), for example the substituents described hereinafter under method (g), these can also be reduced when carrying out method (d).

e) Furthermore, a pyridine derivative of the above-given general formula (VII) can be converted, by treatment with nitrous acid, into an end product of the above-given general formula (I) which contains a hydroxyl group in the 4'-position. The conditions for this reaction are described, for example, in Houben-Weyl, *ed.cit.*, Volume 11/2 (1958), pages 133—157. For this method, there are used compounds of general formula (VII) or the salts thereof which preferably contain, as substituent R^{12} , a free amino group or an amino group substituted with a triphenyl-methyl group or with acyl radicals, such as *o*-nitrophenylsulphenyl, 1-adamantyl-oxy-carbonyl or *tert*-butoxy-carbonyl radicals. In general, there can hereby be used starting materials which contain acyl radicals on the amino group R^{12} , which can easily be split off in acidic media. In carrying out this method, an amino group contained in the side chain R^2 may also be converted into a hydroxyl group.

The following compounds are mentioned as examples of starting materials (VII): 2 - methyl - 3 - hydroxy - 4 - aminomethyl - 5 - methylthiomethyl - pyridine; 2 - methyl - 3 - hydroxy - 4 - aminomethyl - 5 - carbethoxymethylthiomethyl - pyridine; 2 - methyl - 3 - hydroxy - 4 - (*o* - nitrophenylsulphenylaminomethyl) - 5 - aminoethylthiomethyl - pyridine; 2 - methyl - 3 - hydroxy - 4 - (1 - adamantyloxycarbonylaminomethyl - 5 - acetyl thiomethyl - pyridine; 2 - methyl - 3 - hydroxy - 4 - tritylaminomethyl - 5 - (β - carboxy - β - aminoethylthiomethyl) - pyridine; 2 - methyl - 3 - hydroxy - 4 - (*tert* - butoxycarbonylaminomethyl) - 5 - chloroethylthiomethyl - pyridine.

The starting materials (VII) can be obtained, for example, by the reaction of pyridoxamine with 66% hydrobromic acid to give 5'-bromopyridoxamine which is further reacted with appropriate halides or azides, such as 1-adamantyl-oxy-carbonyl chloride, trityl chloride or *o*-nitrosulphenyl chloride, in aqueous solution or, for example, with *tert*-butoxycarbonyl azide in, for example, 50% aqueous dioxan to give the corresponding 5'-bromopyridoxamine substituted in the amino group. These can then be converted into the desired starting materials (VII) by thioalkylation or -acylation.

f) From a 5-thiomethyl derivative of the above-given general formula (III) in which X is a hydrogen atom or an alkali metal or alkaline earth metal cation, there can also be prepared a compound of the above-given general formula (I) by the addition thereto of an alkene or alkyne, which can be substituted by halogen, hydroxy, C_1-C_4 , alkoxy, mercapto, C_1-C_4 alkylthio, optionally functionally changed carboxy and/or $-\text{NR}^3\text{R}^1$.

The compounds (III) may also be added to alkene or alkynes which contain undesired substituents. The undesired substituents can be subsequently split off or converted into desired substituents.

In the case of this method according to the present invention, the mercapto compounds (III) are preferably added to unsaturated carbonyl compounds, whereby the carbonyl groups are thereafter, if desired, removed or can be converted into desired substituents. The α,β -unsaturated carboxylic acids, especially C_1-C_4 α,β -unsaturated carboxylic acids or the functional derivatives thereof, for example, their esters or nitriles, such as acrylic acid, methyl and ethyl acrylate, acrylonitrile, methacrylic acid and its esters and nitrile, crotonic acid and crotonitrile, are especially suitable for the addition. Furthermore, there can be used, as addition components, other α,β -unsaturated carbonyl compounds, for example, α,β -unsaturated ketones such as methyl

vinyl ketone, or α,β -unsaturated carbonyl compounds, such as acrolein.

Furthermore, the mercapto compounds can be added to triple unsaturated, optionally functionally suitably substituted hydrocarbons, especially on to acetylene derivatives, such as propargyl aldehyde, propargyl alcohol, propargyl halides, especially propargyl chloride and bromide, vinyl-acetylene, propargylic acid and the functional derivatives of propargylic acid.

Furthermore, Schiff's bases, especially Schiff's bases from C_1-C_4 aliphatic aldehydes and C_1-C_4 primary or secondary alkylamines can be used as addition components to the mercapto compounds (III).

Undesired substituents in the alkenes or alkynes used for the addition can be removed after the addition or converted into desired substituents, as is described hereinafter under (g).

The addition reactions of the mercapto compounds (III) to alkenes or alkynes are carried out according to the methods described in Houben-Weyl's "Methoden der Organischen Chemie, 4th edition, Volume 9 (1955), pages 120-133. In the case of this method according to the present invention, there are obtained compounds (I) in which R^2 signifies an alkyl radical, which may be substituted in the manner defined in general formula (I) but, in the present case, this alkyl radical contains at least 2 carbon atoms.

g) According to the present invention, compounds of the above-given general formula (I) and the salts thereof can also be prepared in that undesired substituents in the radical R^2 are removed or converted into desired substituents and/or undesired carbon-carbon double bonds or triple bonds are hydrogenated. Furthermore, desired substituents which are not contained in the radical R^2 and/or carbon-carbon multiple bonds can, if desired, be introduced.

g₁) For example, undesired halogen atoms, hydroxyl groups and carbonyl groups present in the radical R^2 can be split off or reduced to hydrogen atoms.

The splitting off of an undesired halogen atom, for example, the conversion of a compound of the above-given general formula (I) which contains the radical $R^2 = -CH_2 \cdot Hal$, especially bromomethyl or chloromethyl, into the corresponding compound (I) in which R^2 is a methyl radical, can be carried out with the use of the reduction agents normally employed for the removal of halogen atoms, for example, with zinc/dilute hydrochloric acid in alcoholic solution or with sodium in alcohols or with sodium amalgam/water or with complex metal hydrides, especially lithium aluminium hydride or sodium borohydride. Furthermore, according to the present invention, a halogen atom can also be removed by catalytic hydrogenation. As catalysts there can be used the conventional heavy metal and noble metal catalysts, especially palladium-calcium carbonate (containing 2.5% palladium), or palladium-charcoal (containing 5% palladium). The conditions for this reduction are described in Weygand-Hilgetag, *ed.cit.*, pages 169-172; F. Zymalkowski, *Katalytische Hydrierung im organisch-chemischen Laboratorium*, F. Enke Verlag, Stuttgart, 1965, pages 158-161; *Org. Syntheses Coll. Vol. 4*, page 509, Interscience Publ., New York, 1963; N.G. Gaylord, *Reductions with Complex Metal Hydrides*, Interscience Publ., New York, 1965, pages 889-917; A. Hajos, *Komplexe Hydride*, VEB Deutscher Verlag der Wissenschaft, Berlin, 1966, pages 219 and 267.

An undesired hydroxyl group in the radical R^2 can be removed by reduction with non-noble metals/acids, especially with zinc/acetic acid or dilute hydrochloric acid or also catalytically, for example, under the conditions described by R. L. Augustine, *Catalytic Hydrogenation, Techniques and Applications in Organic Synthesis*, Edward Arnold Publishers, London, 1965, pages 135-139; Weygand-Hilgetag, *ed.cit.*, pages 177-178.

The hydroxyl group may also be removed after previous esterification with a sulphonic acid, especially *p*-toluene-sulphonic acid. For example, this method can be carried out under the conditions described by L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, page 1032, J. Wiley & Sons, Inc., New York, 1967.

Insofar as in the radical R^2 there is an undesired carbonyl group—especially as a component of an aldehyde or keto grouping—this can be reduced by the methods known for the reduction of carbonyl groups. A carbonyl group can, for example, be reduced by the following methods: catalytically, for example, with platinum oxide or Raney nickel, or also with sodium/absolute alcohol; zinc dust in acid or alkaline solution, complex metal hydrides, especially lithium aluminium hydride in the presence of aluminium chloride. The conditions which can be used in the case of this reduction are described, for example, in Weygand-Hilgetag, *ed.cit.*, pages 178-181; F. Zymalkowski, *Katalytische Hydrierung im organisch-chemischen Laboratorium*, *ed.cit.*,

pages 158—161; R. L. Augustine, *Catalytic Hydrogenation, Techniques and Application in Organic Synthesis*, *ed.cit.*, pages 135—139; A. Hajos, *Komplexe Hydride*, *ed.cit.*, 1966, pages 295—306.

Lithium aluminium hydride-aluminium chloride is preferably used as reducing agent. There may also be used organo-tin hydrides, especially diphenyl-tin hydride and di-*n*-butyl-tin hydride, as well as diphenylsilane and a trialkyl-borane, as reduction agent. The conditions for this reduction are described, for example, in H. Hajos, *Komplexe Hydride*, *ed.cit.*, pages 288—290.

The addition of hydrogen to undesired multiple bonds in the side chain can be carried out with the help of the catalysts usually employed for hydrogenation and under atmospheric pressure in apparatus suitable for this purpose. The more detailed conditions for these reactions are described in R. L. Augustine, *Catalytic Hydrogenation*, *ed.cit.*, pages 135—139; F. Zymalkowski, *Katalytische Hydrierung im organisch-chemischen Laboratorium*, *ed.cit.*, pages 158—161.

Furthermore, if desired, a carbon-carbon triple bond possibly present in the radical R^2 can be saturated with hydrogen either to give a carbon-carbon double bond or to give a saturated carbon-carbon bond. The conditions for this reduction are described in more detail in the above-mentioned works by R. L. Augustine, pages 135—139 and of F. Zymalkowski, pages 158—161.

Finally, for the addition of hydrogen to undesired multiple bonds, there can also be used chemical reducing agents, for example, non-noble metals, especially sodium, in alcohol, sodium or aluminium amalgam in water, alkali metals or alkaline earth metals in liquid ammonia or lithium in organic amines, as described in more detail in Weygand-Hilgetag, *ed.cit.*, pages 116—126. Furthermore, complex metal hydrides, especially lithium aluminium hydride and sodium borohydride can be used as reducing agents, the use of which are described in detail in N. G. Gaylord and Hajos, *ed.cit.*, as well as, in particular, in H. C. Brown, *Hydroboration*, New York, 1962.

g_2) In the side chain R^2 of a pyridine derivative (I) there can, according to the present invention, also be introduced, if desired, carbon-carbon multiple bonds by means of the methods known for the formation of carbon-carbon double and triple bonds.

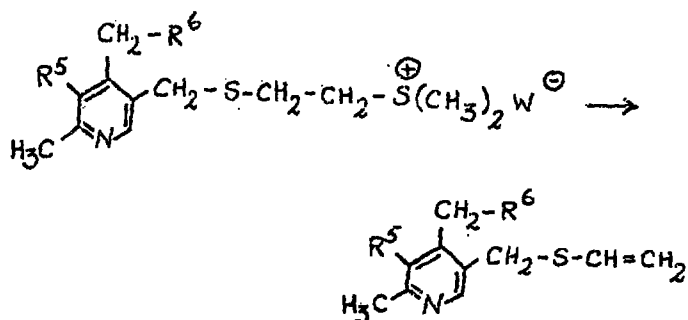
For example, a carbon-carbon double bond can be introduced by splitting off the elements of water, of an alcohol or of a hydrohalic acid from a compound (I), the radical R^2 of which contains undesired hydroxyl, alkoxy or halogen substituents. When 2 of these undesired substituents are present on each of two adjacent carbon atoms of the side chain R^2 , a carbon-carbon triple bond can be introduced into the side chain R^2 by the splitting off thereof.

In the case of splitting off the element of water, it is usual to work in an aqueous solution with the addition of, for example, sulphuric acid, potassium hydrogen sulphate, zinc chloride, phosphorus pentoxide, boric acid, oxalic acid, formic acid, acetyl chloride, a Grignard reagent or iodine and possibly at an elevated temperature. The more detailed conditions under which these reactions can be carried out are described, for example, in Weygand-Hilgetag, *ed.cit.*, pages 782—788.

The removal of the elements of a hydrohalic acid takes place by the use of an inorganic or organic basic substance, such as anhydrous alkali metal alcoholates, solid alkali metal hydroxides, solutions of alkali metal hydroxides in water or organic solvents, alkali metal salts of weak acids, as well as organic bases, such as pyridine, aniline, dimethyl-aniline and quinoline. The conditions under which these reactions can be carried out are described, for example, in Weygand-Hilgetag *ed.cit.*, pages 788—790.

If the radical R^2 in a compound of general formula (I) contains an ether grouping, for example, an acetal or ketal, then, by the use of certain acidic reagents, such as 85% phosphoric acid, alcohol can be split off with the formation of a carbon-carbon double bond. The conditions under which this reaction can be carried out are described in more detail in, for example, *Organikum*, 2nd edition, VEB Deutscher Verlag der Wissenschaften, Berlin, 1963, pages 137—203 and in *Annalen der Chemie*, Volume 656, pages 97—102 (1962).

A carbon-carbon double bond in the R^2 side chain can also be obtained by the splitting off of thioethers from a tertiary sulphonium compound by means of the usual processes (c.f. S. Patai, *The Chemistry of Alkenes*, Interscience Publishers, New York, 1964, page 155 *et. seq.*), especially by the splitting off of, for example, dimethyl sulphide from tertiary sulphonium salts, the third ligand of which is the radical R^2 . By way of example, there is given the following reaction:—



In the above equation, R^5 , R^6 and W^- have the same meanings as above. Instead of the ethylene chain, there can also be compounds with a longer alkylene chain.

A desired double bond in the side chain R^2 can, finally, also be introduced by a condensation reaction, in which a compound (I) with a reactive group which is suitably functional for the carrying out of the condensation reaction is reacted with a second compound which is also suitable for the condensation reaction, with the formation of a double bond and simultaneous chain lengthening. For this purpose, there can be used, in particular, the aldol, Knoevenagel and Wittig reactions. As starting material, there is used a compound of general formula (I) which, however, contains in the side chain R^2 , an undesired CO group.

The reaction conditions under which this reaction can be carried out are described in more detail in Houben-Weyl, *ed.cit.*, Volume 7/1 (1954), pages 76—92 for the carrying out of the aldol condensation; in G. Jones, *The Knoevenagel Condensation*, in Organic Reactions, Volume 15, published by A. C. Cope, J. Wiley & Sons, New York (1967) for the carrying out of the Knoevenagel condensation; and in Johnson, *Ylid Chemistry*, Academic Press, New York, 1965, for the carrying out of the Wittig reaction.

g.) According to the present invention, halogen atoms can be introduced in the side chain R^2 by the addition of hydrogen halides or of halogens to carbon-carbon multiple bonds or by the addition of a hypohalite, whereby, together with the halogen, a hydroxyl group is also introduced, or by the halogenation of undesired hydroxyl or CO groups.

The addition of chlorine or bromine to a compound (I) with an unsaturated side chain R^2 is advantageously carried out in an inert solvent, especially in carbon tetrachloride or chloroform, by the passing in of the calculated amount of gaseous chlorine or by the addition of the calculated amount of bromine in the same solvent. The conditions under which this can be carried out are described in more detail in, for example, Houben-Weyl, *ed.cit.* Volume 5/3 (1962), pages 529—551 and Volume 5/4 (1960), pages 38—100. The conditions for the addition of hypohalic acids are described in more detail in Houben-Weyl, *ed.cit.*, Volume 5/3 (1962), pages 760—780 and Volume 5/4 (1960), pages 133—141 and 540. The process conditions for the addition of hydrogen halides are described in more detail in Houben-Weyl, *ed.cit.*, Volume 5/3 (1962), pages 811—829; Volume 5/4 (1960); pages 102—132 and 535.

Furthermore, halogen substituents can also be introduced by the halogenation of compounds of the general formula (I) which contain undesired hydroxyl or CO groups in the radical R^2 by exchanging the hydroxyl group or the oxygen in the CO group for halogen. For substitution reactions of this type, there can be used a number of different reagents, for example, for the replacement of hydroxyl by chlorine, sulphur halides, such as disulphur dichloride, sulphur dichloride and thionyl chloride; the chlorine compounds of phosphorus and nitrogen, such as phosphorus pentachloride, phosphorus trichloride, phosphorus oxychloride, nitrosyl chloride and nitryl chloride; as well as a few other inorganic and organic chloro compounds. The more detailed carrying out of the reaction is described in the literature, for example, in Houben-Weyl, *ed.cit.*, Volume 5/3, pages 564—960 for chlorine and in Volume 5/4 of this work, pages 610—629, 638, 361—409, for bromine and iodine. The carrying out of such reactions is also described in detail in Weygand-Hilgetag, *ed.cit.*, pages 298—323.

The conversion of undesired carbonyl groups into geminal dihalides, such as 1,1-dihalides, especially $=\text{CCl}_2$ and $=\text{CBr}_2$, can be carried out by the action of inorganic halides, for example, phosphorus pentachloride or phosphorus pentabromide. The conditions under which the reactions are carried out are described in more detail

in, for example, Weygand-Hilgetag *ed.cit.*, pages 334—335 and in Houben Weyl *ed.cit.*, Volume 5/3 page 912 and in Volume 5/4, page 434.

g₄) A hydroxyl group can be introduced into the radical R² of a compound (I) by the addition of water to undesired carbon-carbon multiple bonds or by the reduction of CO groups or of free or esterified COOH groups or of an epoxy grouping or by the action of H-acid compounds on an epoxy bond.

The introduction of a hydroxyl group by the addition of water to carbon-carbon double and triple bonds can be carried out, for example, under the conditions described in more detail in Weygand-Hilgetag, *ed.cit.*, pages 359—365, as well as in B. A. Krenzel, Fortschritte der Chemie (Russian), 20, 759—775 (1951), F. A. Asinger, Chemie und Technologie der Monoolefine, Akademie-Verlag, Berlin, 1957; R. A. Raphael, Actylenic Compounds in Organic Synthesis, Butterworths, London, 1955; and F. Bohlmann, Struktur und Reaktionsfähigkeit der Actylenbindung, Angew. Chemie, 69, 82—86 (1957).

Furthermore, the hydroxyl groups in the radical R² can also be formed by the reduction of CO groups. As reducing agents, there can be used for this purpose the reagents of the Meerwein-Ponndorf-Verley reaction, i.e. aluminium triisopropylate in anhydrous isopropanol, as well as complex metal hydrides, especially lithium aluminium hydride and sodium borohydride, and non-noble metals together with acids, especially zinc in acetic acid, as well as catalytically activated hydrogen, for example, with the use of platinum oxide, platinum black and other known catalysts. The conditions under which it is hereby possible to work are described in more detail in Weygand-Hilgetag, *ed.cit.*, pages 154—169; as well as, particularly, in "Neuere Methoden der präparativen organischen Chemie", published by W. Foerst, Volume 1, pages 137—154, Verlag Chemie, Weinheim, 3rd edition, 1949 (details of the Meerwein-Ponndorf-Verley reductions), in A. Hajos, *ed.cit.*, pages 126, 230, 240 and 279; N. G. Gaylord, *ed.cit.*, pages 107—124 (reductions with complex hydrides); as well as in F. Zymalkowski, *ed.cit.*, pages 91—103; and R. L. Augustine, *ed.cit.*, pages 85—88 (catalytic hydrogenation of the CO group to CHOH).

Furthermore, according to the present invention, the reduction of a free or suitably functionally changed carboxyl group, especially as esterified carboxyl group, in the radical R² of a compound (I) can lead to a desired hydroxyl group. For the carrying out of reactions of this kind, there can be used sodium and an alcohol, for example, ethanol or amyl alcohol, or, in particular, complex metal hydrides. The conditions under which it is hereby possible to work are described in more detail in Organic Syntheses, *ed.cit.*, Coll. Vol. II, pages 154 and 372, as well as Coll. Vol. III, page 671; in N. G. Gaylord, *ed.cit.*, pages 322—638; and in A. Hajor, *ed.cit.*, pages 158, 258, 285, 298, 310 and 349. Finally, as a further process which can be used for the reduction of carboxyl groups to hydroxyl groups, there can be used catalytic hydrogenation, especially with copper chromium oxides (copper chromite) or Raney nickel. In this case, there can be used the conditions described in Weygand-Hilgetag, *ed.cit.*, pages 184—187.

Furthermore, in the radical R² of a compound (I), a hydroxyl group can be introduced by the reduction of an epoxy grouping in the radical R², for example, with non-noble metals and dilute acids, but especially with complex metal hydrides. The more detailed conditions for the carrying out of reactions of this type are described in N. G. Gaylord, *ed.cit.*, pages 646—673; and A. Hajos, *ed.cit.*, pages 149—155. Finally, according to the present invention, a ring opening of the epoxide can also be carried out by the action of compounds containing active hydrogen, which, with extension of the side chain, leads to compounds according to the present invention with a hydroxyl-substituted R² radical. It is also possible simultaneously to introduce other, additionally functional groups into the radical R².

For example, by the action of an alcohol on an undesired epoxy bond in the radical R² of a compound (I), there is formed, by splitting of the epoxide ring, a hydroxyl group, with the simultaneous introduction of an alkoxy radical into the substituent R². Further suitable reaction components for the formation of a hydroxyl group from an epoxy bond are mercaptans, amines, carboxylic acids and Grignard reagents.

g₅) According to the present invention, an alkoxy group can be introduced into the radical R² of a compound (I) by the addition of an alcohol to an undesired carbon-carbon double or triple bond in the radical R².

In this case, working is carried out under the conditions described in more detail in Weygand-Hilgetag, *ed.cit.*, pages 372—376. A hydroxyl group already present in the radical R² can possibly also be converted into an alkoxy radical by alkylation under

the conditions described in method (b) or in Houben-Weyl, *ed.cit.*, Volume 6/3, pages 10—49.

g₆) An —SH or —S-Alkyl group can be introduced into the radical R² in a compound of the above-given general formula (I) by the addition of hydrogen sulphide or of a mercaptan to an undesired carbon-carbon double or triple bond present in the radical R², or by the reduction of an undesired sulphur-oxygen function present in the radical R², this latter resulting in the formation of SH groups. The more detailed conditions for the addition are described in method (f) and in Houben-Weyl, *ed.cit.*, Volume 9 (1955), pages 120—134.

In the case of the reduction of an undesired sulphur-oxygen function, i.e. of a higher oxidation stage of sulphur, in the radical R², there is used, for example, a starting compound of general formula (I) which, however, contains an SO₃H group, especially in esterified form, sulphonic acid halide or anhydride residues, or, for example, contains a sulphinic acid grouping —SO₂H. As reducing agents, there are used non-noble metals and acids but preferably complex metal hydride, the use of which is described in more detail in N. G. Gaylord, *ed.cit.*, pages 851—875.

g₇) A possibly alkylated amino group can be introduced in the radical R² by treatment of a compound of general formula (I) which, however, contains an undesired halogen atom or hydroxyl group in the radical R², with ammonia or hexamethylene-tetramine or with an amine or by the addition of amino compounds to undesired carbon-carbon multiple bonds or by the reduction of appropriate undesired substituents, such as —ON, —NO₂, —NO, =NOH or —NHNH₂, in the radical R².

In the case of the reaction with ammonia, hexamethylene-tetramine or primary or secondary amines, there are used the conventional conditions for an N-alkylation. Preferably, compounds of general formula (I) in which the radical R² is substituted by iodine or by bromine, are used as starting materials. In the case of the introduction of an unsubstituted amino group, there is usually employed at least a tenfold excess of ammonia and, generally, the reaction is carried out with the use of alcohols, especially methanol or ethanol, as solvent.

The replacement of an undesired halogen atom by an amino group in the radical R² of a compound (I) can also be carried out with the use of Gabriel's method, with the use of potassium phthalimide. A detailed description of the methods here used is to be found in Weygand-Hilgetag, *ed.cit.*, pages 516—529, as well as in Houben-Weyl, *ed.cit.*, Volume 11/1 (1955), pages 24—96.

Furthermore, the replacement in the radical R² of compounds of general formula (I) of undesired hydroxyl groups by amino, alkylamino or dialkylamino groups is also possible. In this case, the reaction is carried out under the conditions described in more detail in Houben-Weyl, *ed.cit.*, Volume 11/1 (1955), pages 108—236.

If the radical R² contains carbon-carbon multiple bonds, especially in conjugation with activating groups, for example, formyl, keto, sulphonyl, nitro or carbalkoxy groups, then, according to the present invention, the amino groups can also be introduced into the radical R² by the addition of appropriate components, for example, of ammonia and primary and secondary amines, including those of a cyclic nature, such as piperidine, piperazine or ethylene-imine, to these carbon-carbon multiple bonds. The more detailed conditions under which these reactions are carried out are described in Houben-Weyl, *ed.cit.*, Volume 11/1 (1955), pages 267—341.

It is also possible to obtain an —NR³R⁴ group in the radical R² when a compound of general formula (I) which contains, in the radical R², additional undesired groupings which can be reduced to amino, alkylamino or dialkylamino radicals, especially —CN, —NO₂, —NO, =NOH and —NHNH₂ groups. In this case, there are employed the reducing agents normally used for such reductions, especially sodium amalgam, sodium in alcohol, other non-noble metals, for example, zinc with acids, sodium dithionite or complex metal hydrides. The description of such reductions is given in more detail in Houben-Weyl, *ed.cit.*, Volume 11/1, pages 341—730.

g₈) According to the present invention, a carboxyl group is introduced in the radical R² of a compound (I) by the oxidation of undesired substituents, especially of formyl and primary alcoholic hydroxyl groups, or by the hydrolysis of a functionally changed carboxyl group or by other methods of synthesis known for the production of carboxyl groups.

Thus, it is possible to introduce a carboxyl group into the radical R² by the oxidation of suitable, undesired substituents in the radical R², starting from compounds in which the pyridine ring can be protected in the 3- and 4-position. There can be used all conventional oxidation agents. The more detailed conditions are described in

Weygand-Hilgetag, *ed.cit.*, pages 405—407; and in Houben-Weyl, *ed.cit.*, Volume 8 (1952), pages 407—414.

If the radical R^2 already contains an undesired, functionally changed carboxyl group then from this there can be liberated a carboxyl group by the use of saponifying agents. As functional derivatives, there may be mentioned, in particular, acid nitriles, esters, amides, hydrazides, amidines, the halides and the hydroxamic acids. The carrying out of these conversions is described in detail in Houben-Weyl, *ed.cit.*, Volume 8 (1952), pages 418—433.

Finally, according to the present invention, carboxyl groups can be introduced into the side chain by acetoacetic ester and malonic acid synthesis, by the conversion of ketones, fission of nitro compounds, carbon bonding and rearrangement reaction, as are described in more detail in Houben-Weyl, *ed.cit.*, Volume 8 (1952), pages 433—462.

g₉) Free or already functionally changed carboxyl groups in the radical R^2 of a compound (I) can, if desired, be functionally changed.

In particular, free carboxyl groups or carboxylic acid halides can be converted into esters, amides, anhydrides or other functional derivatives. It is also possible to convert esters into amides.

For the esterification of a free carboxylic acid group in the radical R^2 of a compound (I), there can be used the processes known from the literature, including the esterification with diazoalkanes or the reaction with alkali metal alcoholates (Williamson synthesis). The carrying out of these reactions is described in more detail in Houben-Weyl, *ed.cit.*, Volume 8 (1952), pages 508—628.

For amidation or the introduction of other nitrogen-containing substituents, there can be used reactive functional derivatives of the carboxyl group in the radical R^2 , especially the esters, anhydrides and halides. The conditions under which it is possible to work in the preparation of such functional nitrogen derivatives of the carboxyl group are described in detail in Houben-Weyl, *ed.cit.*, Volume 8 (1952), pages 653—706.

Insofar as in the products which have been obtained by the above-described methods (b)—(g), there are still present protective groups in the hydroxyl groups R^3 and R^6 , these protective groups are split off subsequently to the main process step (b) to (g). For the liberation of these protected hydroxyl groups, working is carried out under the conditions described under method (a). In this case, it is preferable to use dilute acidic or alkaline agents for splitting off the protective groups.

Furthermore, according to the present invention, compounds of general formula (I) in which R^1 signifies a sulphur atom can, if desired, be converted into the corresponding end products in which the substituent R^1 is —SO— by treatment with oxidation agents which are conventionally used for the conversion of thioethers into sulfoxides. As oxidation agents, there are, in particular, used hydrogen peroxide, sodium metaperiodate, per acids, such as phthalic monoperacid or chromic oxide in acids, such as 75% acetic acid, or *tert.*-butyl hypochlorite. The oxidation is expediently carried out under the following conditions:

The compounds (I) in which R^1 is a sulphur atom are dissolved in glacial acetic acid and, after mixing with the calculated amount of 30% hydrogen peroxide, left to stand for a few hours at 0° C. or even at ambient temperature. The oxidation of the compounds (I) in which R^1 is a sulphur atom with sodium periodate advantageously takes place in a water/methanol mixture at ambient temperature. For the oxidation with per acids, there are used temperatures of between about -20° C. and +20° C. and, as solvent, acetone or chloroform. The conditions under which the oxidation with *tert.*-butyl hypochlorite can be carried out as described in more detail in J.Org.Chem., Volume 32(10), 3111 (1967).

An end product obtained according to the present invention can be converted, in the usual manner, into the corresponding acid addition salts. For this reaction, there can be used those acids which give physiologically compatible salts. Thus, there can be used organic and inorganic acids, such as aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- and poly-basic carboxylic and sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethyl-acetic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, amino-carboxylic acids, sulphamic acids, benzoic acid, salicylic acid, phenyl-propionic acid, citric acid, gluconic acid, ascorbic acid, isonicotinic acid, methane-sulphonic acid, ethane-disulphonic acid, β -hydroxy-ethane-sulphonic acid, *p*-toluene-sulphonic acid, naphthalene-mono- and -disulphonic acids, sulphuric acid or hydrobromic acid, or phosphoric acids,

such as orthophosphoric acid and the like. However, it is preferred to use mineral acids, such as hydrochloric acid or sulphuric acid.

According to the present invention, compounds of general formula (I), which have been prepared by one of the above-described methods, can, if desired, be converted into their quaternary ammonium salts and/or tertiary sulphonium salts. This reaction is carried out with the usual alkylation agents (hereinafter referred to as "N,S-dialkylation" or "N- or S-monoalkylation"). The alkylation can be carried out, for example, with alkyl halides, preferably with C_1-C_4 alkyl halides, especially the iodides, such as methyl iodide, ethyl iodide, propyl iodide or allyl iodide, or also with benzyl iodide, and possibly thereafter, an undesired halogen ion, for example an iodine ion, is replaced by a desired halogen ion, for example a chlorine or bromine ion. Sulphuric acid and sulphonic acid esters can also be used for the reaction.

The formation of quaternary ammonium or of tertiary sulphonium salts can be carried out in the presence of a solvent or possibly also without the use of a solvent. Particularly well suited solvents are those with high dielectric constants, such as chloroform, or nitro compounds, such as nitrobenzene or nitromethane, or cyano compounds, such as acetonitrile, or also benzyl alcohol.

The reactions are usually carried out at ambient temperature. However, it is also possible to use elevated temperatures.

The rapidly reacting quaternising agents for example the alkyl iodides, are expediently added in an equimolar amount; the less reactive alkylation agents, for example the alkyl chlorides, are advantageously used in excess.

It is also possible to alkylate selectively. For example, it is possible to carry out the N-alkylation of the compounds (I) with the less reactive alkylation agents.

Generally, for the preparation of quaternary ammonium and/or tertiary sulphonium salts of compounds (I), there are preferred alkylation agents which contain a lower alkyl radical, especially a methyl radical.

By the reaction of a compound (I) in which R^1 is a sulphur atom and R^2 is a methyl radical, there is obtained, for example, 2-methyl-3-hydroxy-4-hydroxymethyl-5-methyl-thiomethyl-pyridinium iodide.

Furthermore, a compound (I) can also be liberated from a corresponding ammonium and/or sulphonium salt. This reaction is brought about by the addition of nucleophilic reagents, especially bases, in inert solvents or by the addition of a basically-reacting solvent.

As nucleophilic reaction components, especially bases, there can be considered: alkali metal mercaptides, such as sodium or potassium mercaptides, which can possibly also be substituted by a hydrocarbon radical, for example, methyl, ethyl or benzyl radicals, sodium or potassium mercaptides, alkali metal thiosulphates, such as sodium or potassium thiosulphate, ammonia or amines, especially aliphatic amines which are liquid at ambient temperature, such as ethylamine, propylamine or benzylamine, or, in particular, ethanolamine. It is also possible to work in the presence of an inert solvent. As inert solvents, there can be used, in particular, alcohols, especially lower alcohols, such as methanol, ethanol, propanol or isopropanol, or acetone or methyl ethyl ketone.

The liberation of the bases (I) from the quaternary ammonium or tertiary sulphonium salts can, for example, be carried out according to the conditions described in Houben-Weyl, *ed.cit.*, Volume 11/1 (1957), pages 966—991 and in *Chemische Berichte*, Volume 90, pages 395 and 403 (1957).

It is also possible to liberate a compound (I) from an undesired acid addition salt by treatment with an alkaline compound, especially with an alkali metal hydroxide, such as sodium or potassium hydroxide, or with an alkaline-reacting salt, such as an alkali metal carbonate, for example sodium or potassium carbonate, and possibly subsequently to convert it into another, desired acid addition salt.

The compounds (I) can be used in admixture with conventional pharmaceutical carriers, possibly together with other active materials.

As carrier substances, there can be used, for example, those organic or inorganic materials which are suitable for parenteral, enteral or topical application and which do not react with the new compounds, such as water, vegetable oils, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talc, petroleum jelly and cholesterol. For parenteral application, there are used, in particular, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants. For enteral application, there can also be used tablets or dragees and for topical application, salves or creams, which can be sterilised or admixed with adjuvants, such as preserving,

stabilising or wetting agents or with salts for influencing the osmotic pressure or with buffer substances.

The new compounds according to the present invention are preferably administered at a dosage rate of from 20 to 500 mg., the preferred dosage units containing 0.1 to 100 mg. of active substance per dosage unit.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1.

11 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine hydrochloride are added to a solution of 6.2 g. potassium hydroxide in 100 ml. methanol and mixed with 7 g. methyl iodide. After standing overnight, the solution is evaporated, mixed with water and extracted with ethyl acetate. The solution is dried over anhydrous sodium sulphate and the solvent evaporated off. The residue of 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine melts, after recrystallisation from alcohol, at 135° C. The yield is 8.7 g. The hydrochloride melts at 155° C. (Decomp.).

EXAMPLE 2.

110 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine hydrochloride are dissolved in a solution of 1000 ml. water and 250 ml. 2N sodium hydroxide and, while stirring, 63 g. dimethyl sulphate and 250 ml. 2N sodium hydroxide are added dropwise simultaneously, in such a manner that the pH value of the solution lies between 7 and 7.5. The temperature of the solution lies between 20 and 25° C. After stirring for 5 hours, the precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine is filtered off with suction and, after drying in a desiccator, treated with alcoholic hydrochloric acid. The precipitated hydrochloride is filtered off with suction and recrystallised from alcohol/ether. It has a melting point of 154—155° C. (decomp.).

EXAMPLE 3.

20 g. *p*-toluene-sulphonic acid methyl ester are dissolved in 220 ml. methanol which contains 8 g. sodium hydroxide, mixed with 22 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine hydrochloride and left to stand for 12 hours at ambient temperature. The solution is evaporated in a vacuum and the residue mixed with water and extracted with ethyl acetate. The solution is dried over anhydrous sodium sulphate. The residue obtained after evaporation of the solvent is treated with alcoholic hydrochloric acid. The precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine hydrochloride is filtered off with suction and recrystallised from alcohol/ether. It has a melting point of 154—155° C. (decomp.).

EXAMPLE 4.

A solution of 18.7 g. 2-methyl-3-hydroxy-4-hydroxy-methyl-5-chloromethyl-pyridine in 200 ml. methanol is slowly added to a solution of sodium mercaptide (prepared by passing methyl mercaptan into a solution of 2.3 g. sodium in 40 ml. methanol) and subsequently boiled under reflux for half an hour. The separated sodium chloride is filtered off with suction, the filtrate evaporated, the residue treated with alcoholic hydrochloric acid and the precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine hydrochloride filtered off with suction. It has a melting point of 153—154° C. (decomp.).

EXAMPLE 5.

A solution of 0.5 g. sodium in 50 ml. isopropanol is first mixed with 2.3 g. dimethylaminoethyl mercaptan and subsequently mixed with 5 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-bromomethyl-pyridine. After heating to 60° C. for one hour, the precipitated sodium bromide is filtered off with suction and hydrogen chloride passed into the filtrate until it has a weakly acidic reaction. After the addition of 5 ml. ether, 2-methyl-3-hydroxy-4-hydroxymethyl-5-dimethylaminoethylthiomethyl-pyridine dihydrochloride precipitates out. The substance is filtered off with suction and recrystallised from methanol/ether. It has a melting point of 200° C. (decomp.).

EXAMPLE 6.

9.2 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine and 7 g. *n*-butyl bromide are added to a solution of 1.2 g. sodium in 100 ml. isopropanol. After

boiling for 1.5 hours under reflux, precipitated sodium bromide is filtered off with suction and hydrogen chloride passed into the filtrate. The precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-*n*-butylthiomethyl-pyridine hydrochloride is subsequently filtered off with suction and recrystallised from alcohol/ether. It has a melting point of 124° C.

EXAMPLE 7.

A solution of 35 g. cysteine monohydrochloride monohydrate in 50 ml. water is warmed to 40° C. Simultaneously, 37.5 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-chloromethyl-pyridine are added portionwise, together with a solution of 22.4 g. potassium hydroxide in 30 ml. water. The temperature thereby increases to 68° C. After 30 minutes, the reaction mixture is cooled and the precipitate formed is filtered off with suction. For purification, this precipitate is dissolved in 80 ml. 2N hydrochloric acid and the pH value of the solution adjusted to 5.5 with 2N sodium hydroxide. The S-[2-methyl-3-hydroxy-4-hydroxymethyl-pyridyl-(5)-methyl]-cysteine which precipitates out overnight is filtered off with suction, washed with water and methanol and dried in a desiccator. It has a melting point of 230° C. (decomp.).

EXAMPLE 8.

A solution of 22 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine hydrochloride in 20 ml. water is mixed with 10 ml. of a 35% formaldehyde solution. The 2-methyl-3-hydroxy-4-hydroxymethyl-5-hydroxymethylthiomethyl-pyridine hydrochloride which precipitates out after standing for 12 hours, is filtered off with suction and recrystallised from methanol. The compound has a melting point of 157° C.

EXAMPLE 9.

9.2 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine are dissolved in 50 ml. 1N sodium hydroxide and mixed portionwise, while shaking, with 5 g. dimethylcarbamic acid chloride. The S-[2-methyl-3-hydroxy-4-hydroxymethyl-pyridyl-(5)-methyl]-thioformic acid dimethylamide which separates out overnight, is filtered off with suction and recrystallised from alcohol. It has a melting point of 188° C.

EXAMPLE 10.

S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-thio-acetic acid ethyl ester is prepared in a manner analogous to that described in Example 6 by the reaction of 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptomethyl-pyridine with ethyl chloroacetate. After recrystallisation from alcohol, this compound has a melting point of 96° C. and the corresponding hydrochloride, after recrystallisation from alcohol/ether, has a melting point of 175° C.

EXAMPLE 11.

2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - allylthiomethyl - pyridine is prepared in a manner analogous to that described in Example 1 by the reaction of 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - mercaptomethyl - pyridine hydrochloride with allyl bromide. After recrystallisation from ethyl acetate/hexane, the compound has a melting point of 111° C. The corresponding hydrochloride has a melting point of 136° C.

EXAMPLE 12.

2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - propargylthiomethyl - pyridine is prepared in a manner analogous to that described in Example 1 by the reaction of 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - mercaptomethyl - pyridine with propargyl chloride. After recrystallisation from ethyl acetate/hexane, the compound has a melting point of 140° C. The corresponding hydrochloride has a melting point of 135° C.

EXAMPLE 13.

1.4 g. 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylthiomethyl-pyridine hydrochloride are left to stand for 48 hours at ambient temperature in 30 ml. glacial acetic acid with 0.8 ml. 30% hydrogen peroxide. The solvent is evaporated in a vacuum and the precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylsulphinylmethyl-pyridine hydrochloride is separated and recrystallised from alcohol/ether. It has a melting point of 179° C.

EXAMPLE 14.

21 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-ethylthiomethyl-pyridine in 50 ml. methanol are added to a solution of 23.5 g. sodium metaperiodate in 200 ml. water

which has been cooled to 0° C. The precipitated material is filtered off with suction and the filtrate extracted with ethyl acetate. The solution is dried over anhydrous sodium sulphate and evaporated in a vacuum. The residue is treated with alcoholic hydrochloric acid, the precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-ethylsulphinylmethyl-pyridine hydrochloride is filtered off with suction and recrystallised from alcohol/ether. This compound has a melting point of 143° C.

EXAMPLE 15.

6.6 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine in a mixture of 50 ml. tetrahydrofuran and 80 ml. acetone are mixed, at -10 to -15° C., with a solution of 6.1 g. phthalic monoperacid in 180 ml. ether which has been cooled to -15° C. After 24 hours, the solvent is evaporated. The residue is extracted with chloroform and filtered free of undissolved phthalic acid. After evaporation of the chloroform, the residue obtained is treated with alcoholic hydrochloric acid, the precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylsulphinylmethyl-pyridine hydrochloride is filtered off with suction and recrystallised from alcohol/ether. It has a melting point of 173—179° C.

EXAMPLE 16.

5 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine are heated to 80° C. in 30 ml of 75% acetic acid. Subsequently, a solution of 2 g. chromium trioxide in 6 ml. water is added dropwise. The temperature of the reaction mixture is maintained at 70—80° C. for 1 hour. It is then evaporated in a vacuum, the residue is mixed with water and then continuously extracted with ethyl acetate. The ethyl acetate extract is dried over anhydrous sodium sulphate, evaporated and the residue treated with alcoholic hydrochloric acid. The precipitated 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylsulphinylmethyl-pyridine hydrochloride is filtered off with suction and recrystallised from alcohol/ether. It has a melting point of 179° C.

EXAMPLE 17.

2-methyl-3-hydroxy-4-hydroxymethyl-5-allylsulphinyl-methyl-pyridine hydrochloride is prepared in a manner analogous to that described in Example 13 by the reaction of 2-methyl-3-hydroxy-4-hydroxymethyl-5-allylthiomethyl-pyridine hydrochloride with 30% hydrogen peroxide. After recrystallisation from alcohol/ether, the product has a melting point of 140° C. (decomp.).

EXAMPLE 18.

2-methyl-3-hydroxy-4-hydroxymethyl-5-propargyl-sulphinylmethyl-pyridine hydrochloride is prepared in a manner analogous to that described in Example 13 by the reaction of 2-methyl-3-hydroxy-4-hydroxymethyl-5-propargylthiomethyl-pyridine hydrochloride with 30% hydrogen peroxide. After recrystallisation from methanol/ether, the product has a melting point of 158° C. (decomp.).

EXAMPLE 19.

9 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-mercaptopmethyl-pyridine are dissolved in an excess of acetic anhydride, a few ml. of anhydrous pyridine are added thereto and the reaction mixture left to stand overnight in a cooling waterbath. The cooled reaction product is mixed with water which has been acidified to pH 2—3 and heated to 60—80° C. for 30 minutes. After cooling, the aqueous phase is extracted in an extractor with ether. The dried ethereal phase is freed from solvent by allowing a corresponding amount of boiling absolute alcohol to run in. After cooling the alcoholic solution, hydrogen chloride is passed, whereupon, after standing overnight, 2-methyl-3-hydroxy-4-hydroxymethyl-5-acetylthiomethyl-pyridine hydrochloride crystallises out. The yield is 85% of theory. After recrystallisation from alcohol/ether, the product has a melting point of 160° C.

EXAMPLE 20.

9.24 g. isopropylidene-5'-thiopyridoxine are dissolved in 200 ml. ether contained in a round-bottomed flask and mixed with an ethereal solution of diazomethane until the yellow colour remains. After 1 hour, excess diazomethane is removed by the dropwise addition of dilute acetic acid and the solvent then evaporated. The residue

- is mixed with 100 ml. 0.01N hydrochloric acid or sulphuric acid or some other mineral acid and heated on a steam bath for 30 minutes. After cooling, the reaction mixture is extracted several times with ethyl acetate, the extracts combined and dried, the solvent then evaporated and the residue mixed with anhydrous alcohol which has been saturated with hydrogen chloride. Upon standing overnight, 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine hydrochloride crystallises out. The yield is 87% of theory and the product has a melting point of 155° C.

EXAMPLE 21.

- A solution of 1.7 g. lauric acid chloride in 5 ml. chloroform is added dropwise to a solution of 2.0 g. isopropylidene-5'-thiopyridoxine hydrochloride in 20 ml. chloroform and 10 ml. pyridine. After leaving to stand overnight, the reaction mixture is washed in a separating funnel, first with water and then with 0.5N hydrochloric acid. The separated chloroform phase is dried and evaporated. The oily residue (2 g.) is boiled under reflux with 20 ml. water, 40 ml. alcohol and 8 ml. 1N hydrochloric acid for 10 minutes and then freed from solvent in a vacuum. Upon trituration with isopropanol, the residue crystallises. After recrystallisation from ethyl acetate/alcohol, the 2-methyl-3-hydroxy-4-hydroxymethyl-5-laurylthiomethyl-pyridine obtained melts at 118—119° C. By stirring with alcoholic hydrochloride, there is obtained the corresponding hydrochloride, which has a melting point of 125° C.

EXAMPLE 22.

- 11 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-thiomethyl-pyridine hydrochloride are added to a solution of 6.2 g. potassium hydroxide in 150 ml. methanol and subsequently mixed with 8.5 g. β -methylthioethyl bromide. The reaction mixture is heated on a waterbath for 2 hours and then substantially freed from solvent. The residue is extracted with ethyl acetate. The combined ethyl acetate phases are dried over anhydrous sodium sulphate and then evaporated. After the addition of alcoholic hydrochloride, and leaving to stand overnight, 2-methyl-3-hydroxy-4-hydroxymethyl-5-(β -methylthioethylthiomethyl)-pyridine crystallises out as the hydrochloride.

EXAMPLE 23.

- A cooled solution of 6.1 g. ethylene sulphide in alcohol is added dropwise, in the course of 1 hour, to a well stirred and ice-cooled solution of 18.5 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-thiomethyl-pyridine in a mixture of 2.5 g. sodium and 200 ml. absolute alcohol and stirring subsequently continued for one hour at ambient temperature. After evaporation of the solvent, the residue is acidified with acetic acid and dry hydrogen chloride passed in, whereupon, upon standing in a refrigerator overnight, 2-methyl-3-hydroxy-4-hydroxymethyl-5-(thioethylthiomethyl)-pyridine crystallises out.

EXAMPLE 24.

- 60 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-thiomethyl-pyridine are added portionwise, with stirring and ice cooling, to 180 ml. ethylene-imine in such a manner that the temperature does not exceed +10° C. After completion of the addition, the reaction mixture is stirred for a further 2 hours, while cooling. The precipitated reaction product is filtered off with suction, washed with ether (m.p. of the base 156—158° C.) and, by suspension in alcoholic hydrochloric acid, converted into the hydrochloride of 2-methyl-3-hydroxy-4-hydroxymethyl-5-(β -aminoethylthiomethyl)-pyridine which, after recrystallisation from methanol/ether, melts at 212° C.

EXAMPLE 25.

- 22 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-thiomethyl-pyridine hydrochloride are suspended in 200 ml. ethanol and 12.4 potassium hydroxide added, while stirring. Stirring is continued for a further hour, the solution is filtered and the filtrate then mixed with 17 g. isopropyl iodide. After leaving to stand overnight, precipitated potassium iodide is filtered off with suction, the filtrate is evaporated in a vacuum and the residue is dissolved in alcoholic hydrochloric acid. The crude 2-methyl-3-hydroxy-4-hydroxymethyl-5-(isopropylthiomethyl)-pyridine hydrochloride thus obtained melts, after recrystallisation from methanol/ether, at 135—136° C. The yield is 21 g.

EXAMPLE 26.

39.6 g. thioacetic acid are added to a solution of 29 g. potassium hydroxide in 300 ml. methanol. Then, while cooling with ice, 68 g. isopropylidene-5'-chloropyridoxine hydrochloride are added to the solution and the mixture left to stand overnight.

The separated potassium chloride is filtered off with suction on a sintered glass plate and the filtrate evaporated to dryness in a vacuum. The residue is mixed with alcoholic hydrochloric acid and ether. 70 g. (96% of theory) 3,4'-isopropylidene-5-acetylthiomethylpyridoxine crystallise out in the form of the hydrochloride, which has a melting point of 180° C.

For splitting off the isopropylidene group, the residue of the vacuum evaporation is mixed with 300 ml. 0.01N sulphuric acid and the mixture heated on a steam bath for 30 minutes. The cooled solution is then extracted with ether, the extract solution dried, evaporated and the evaporation residue mixed with alcoholic hydrochloric acid and left to stand overnight in a refrigerator. There is obtained a 76% yield of 2-methyl-3-hydroxy-4-hydroxymethyl-5-acetylthiomethyl-pyridine hydrochloride, which has a melting point of 160° C.

EXAMPLE 27.

8 g. 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylsulphonylmethyl-pyridine-N-oxide are dissolved in glacial acetic acid; then, with gentle warming on a water bath, 24 g. zinc dust are introduced. After subsidence of the evolution of hydrogen, the reaction vessel is equipped with a magnetic stirrer and the reaction mixture stirred for 24 hours, while heating to 100° C. After cooling, excess zinc dust is filtered off and the glacial acetic acid evaporated. The residue is extracted several times with hot, absolute alcohol. After cooling the combined extracts, hydrogen chloride is passed in and 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine precipitates out in the form of the hydrochloride which has a melting point of 155° C. (decomp.).

EXAMPLE 28.

18.1 g. 2 - methyl - 3 - hydroxy - 4 - (1 - adamantyloxycarbonylaminoethyl)-5-thiomethyl-pyridine are dissolved in 50% dioxan. Subsequently, an equivalent amount (5.11 g.) of pivalic acid (2,2,2-trimethyl-acetic acid) are added thereto, whereupon 10.35 g. dicyclohexyl-carbodiimide, dissolved in 45 ml. 50% dioxan, are added dropwise, while stirring. After 4 hours, precipitated dicyclohexyl-urea is filtered off and the solvent evaporated off from the filtrate in a vacuum at the lowest possible temperature. As residue, there remains behind crude 2-methyl-3-hydroxy-4-(1-adamantyl-oxycarbonylaminoethyl-5-pivalylthiomethyl-pyridine, which is taken up in 2N hydrochloric acid, after which 11 g. sodium nitrite are added. After the evolution of nitrogen ceases, the reaction mixture is stirred for a further hour at ambient temperature and then extracted with ethyl acetate. The dried solution is freed from solvent and the residue taken up with ethanolic hydrochloric acid. Upon standing overnight in a refrigerator, 2-methyl-3-hydroxy-4-hydroxymethyl-5-pivalylthiomethyl-pyridine hydrochloride crystallises out.

EXAMPLE 29.

10.1 g. acrylic acid methyl ester are added dropwise, with stirring, to a solution of 18.5 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-thiomethyl-pyridine in absolute alcohol containing 4 g. sodium methylate at such a rate that, if necessary with external cooling, the temperature of the reaction vessel can be maintained at 50° C. $\pm$ 5° C. At the end of the addition, the reaction mixture is heated, while stirring, for 2 hours at 50° C. in order to complete the reaction. The reaction mixture is subsequently cooled, filtered if necessary, evaporated to about one third of its original volume and the solution then saturated with dry hydrogen chloride. The precipitated mixture of sodium chloride and ester hydrochloride is washed free of salt with the smallest possible amount of water and then recrystallised from alcoholic hydrochloric acid. There is thus obtained pure 2-methyl-3-hydroxy-4-hydroxymethyl-5-(carbo-methoxyethylthiomethyl)-pyridine hydrochloride.

EXAMPLE 30.

8.7 g. vinyl acetate are mixed portionwise, with ice cooling, with 18.5 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-thiomethyl-pyridine and the mixture thereafter left to stand overnight. Upon trituration with ether, the reaction mixture crystallises and is then filtered off with suction, washed with ether and recrystallised from methanol. The 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - acetoxylethylthiomethyl) - pyridine thus obtained melts at 224° C.

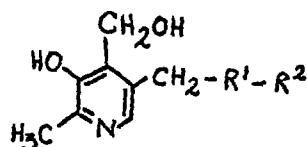
EXAMPLE 31.

2 g. 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridine are dissolved in 30 ml. acetonitrile. The solution is mixed with 1.3 g. methyl iodide and left to stand for 3 days and thereafter filtered free of precipitate. The filtrate is evaporated.

The crystals which separate upon standing overnight in a refrigerator are filtered off with suction and washed with a little cold methanol. After recrystallization from methanol, the 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridinium methyl iodide obtained melts at 165° C. the yield is 0.8 g.

WHAT WE CLAIM IS:—

1. Sulphur-containing pyridine derivatives of the general formula:—



wherein

R¹ is a sulphur atom or an —SO—group;

R² is an acyl radical containing up to 4 carbon atoms, —CO . NR³R⁴, an unsaturated aliphatic hydrocarbon radical containing up to 4 carbon atoms or an alkyl radical which may be substituted by at least one member selected from halogen atoms, hydroxyl and mercapto groups, alkoxy radicals containing up to 4 carbon atoms, alkylthio radicals containing up to 4 carbon atoms, and free and functionally changed carboxy and/or —NR³R⁴ groups with the proviso that R² is a radical other than ethyl, β-chloroethyl or β-hydroxyethyl when R¹ is a sulphur atom; and

R³ and R⁴, which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 4 carbon atoms or together form a 5- or 6-membered alkylene chain which may be interrupted by at least one member selected from nitrogen, oxygen and sulphur atoms; and the acid-addition salts, quaternary ammonium salts and tertiary sulphonium salts thereof.

2. Compounds according to claim 1, wherein R¹ is a sulphur atom and R² is an acetyl, —CONH₂, —CO . N(CH₃)₂, —CO . N(C₂H₅)₂, vinyl or propargyl radical or an alkyl radical containing up to 4 carbon atoms which may be substituted by at least one member selected from chlorine, bromine, hydroxyl, mercapto, methylthio, dimethylamino, diethylamino, amino, carboxyl, methoxy-carbonyl and ethoxycarbonyl radicals.

3. Compounds according to claim 1, wherein R¹ is a sulphur atom and R² is a —CH₂—CH=CH₂, —CH(CH₃)₂, —n—C₄H₉, —CH₂OH, —(CH₂)₂—SH, —(CH₂)₂—SCH₃, —CH₂ . CH(NH₂)COOH, —(CH₂)₂—NH₂, —(CH₂)₂N(CH₃)₂ or —CH₂ . COOC₂H₅ group.

4. Compounds according to claim 1, wherein R¹ is an —SO— group and R² is a —CH₃, —C₂H₅, —CH₂—CH=CH₂ or —CH₂—C≡CH group.

5. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylthiomethyl - pyridine.

6. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - β - dimethylaminoethylthiomethyl-pyridine.

7. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - n - butylthiomethyl-pyridine.

8. S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-cysteine.

9. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - hydroxymethylthiomethyl-pyridine.

10. S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-thioformic acid dimethylamide.

11. S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-thio-acetic acid ethyl ester.

12. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - allylthiomethyl-pyridine.

13. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - propargyl - thiomethyl-pyridine.

14. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylsulphinylmethyl-pyridine.

15. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - ethylsulphinylmethyl-pyridine.

16. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - allylsulphinylmethyl-pyridine.

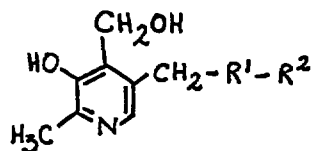
17. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - acetylthiomethyl-pyridine.

18. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - laurylthiomethylpyridine.

The crystals which separate upon standing overnight in a refrigerator are filtered off with suction and washed with a little cold methanol. After recrystallization from methanol, the 2-methyl-3-hydroxy-4-hydroxymethyl-5-methylthiomethyl-pyridinium methyl iodide obtained melts at 165° C. the yield is 0.8 g.

WHAT WE CLAIM IS:—

1. Sulphur-containing pyridine derivatives of the general formula:—



wherein

R^1 is a sulphur atom or an $-\text{SO}-$ group;

R^2 is an acyl radical containing up to 4 carbon atoms, $-\text{CO} \cdot \text{NR}^3\text{R}^4$, an unsaturated aliphatic hydrocarbon radical containing up to 4 carbon atoms or an alkyl radical which may be substituted by at least one member selected from halogen atoms, hydroxyl and mercapto groups, alkoxy radicals containing up to 4 carbon atoms, alkylthio radicals containing up to 4 carbon atoms, and free and functionally changed carboxy and/or $-\text{NR}^3\text{R}^4$ groups with the proviso that R^2 is a radical other than ethyl, β -chloroethyl or β -hydroxyethyl when R^1 is a sulphur atom; and

R^3 and R^4 , which may be the same or different, are hydrogen atoms or alkyl radicals containing up to 4 carbon atoms or together form a 5- or 6-membered alkylene chain which may be interrupted by at least one member selected from nitrogen, oxygen and sulphur atoms; and the acid-addition salts, quaternary ammonium salts and tertiary sulphonium salts thereof.

2. Compounds according to claim 1, wherein R^1 is a sulphur atom and R^2 is an acetyl, $-\text{CONH}_2$, $-\text{CO} \cdot \text{N}(\text{CH}_3)_2$, $-\text{CO} \cdot \text{N}(\text{C}_2\text{H}_5)_2$, vinyl or propargyl radical or an alkyl radical containing up to 4 carbon atoms which may be substituted by at least one member selected from chlorine, bromine, hydroxyl, mercapto, methylthio, dimethylamino, diethylamino, amino, carboxyl, methoxy-carbonyl and ethoxycarbonyl radicals.

3. Compounds according to claim 1, wherein R^1 is a sulphur atom and R^2 is a $-\text{CH}_2-\text{CH}=\text{CH}_2$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}_4\text{H}_9$, $-\text{CH}_2\text{OH}$, $-(\text{CH}_2)_2-\text{SH}$, $-(\text{CH}_2)_2-\text{SCH}_3$, $-\text{CH}_2 \cdot \text{CH}(\text{NH}_2)\text{COOH}$, $-(\text{CH}_2)_2-\text{NH}_2$, $-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ or $-\text{CH}_2 \cdot \text{COOC}_2\text{H}_5$ group.

4. Compounds according to claim 1, wherein R^1 is an $-\text{SO}-$ group and R^2 is a $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, $-\text{CH}_2-\text{CH}=\text{CH}_2$ or $-\text{CH}_2-\text{C}\equiv\text{CH}$ group.

5. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylthiomethyl - pyridine.

6. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - β - dimethylaminoethylthiomethyl-pyridine.

7. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - n - butylthiomethyl-pyridine.

8. S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-cysteine.

9. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - hydroxymethylthiomethyl-pyridine.

10. S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-thioformic acid dimethylamide.

11. S - [2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - pyridyl - (5) - methyl]-thio-acetic acid ethyl ester.

12. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - allylthiomethyl-pyridine.

13. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - propargyl - thiomethyl-pyridine.

14. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylsulphinylmethyl-pyridine.

15. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - ethylsulphinylmethyl-pyridine.

16. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - allylsulphinylmethyl-pyridine.

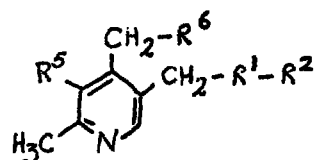
17. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - acetylthiomethyl-pyridine.

18. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - laurylthiomethylpyridine.

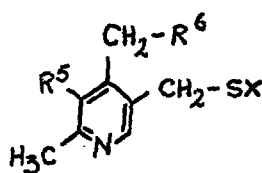




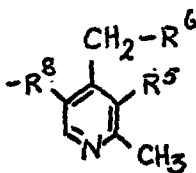
19. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - methylthioethylthio-methyl)-pyridine.
20. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (thioethylthiomethyl)-pyridine.
- 5 21. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - aminoethyl) - thio-methyl-pyridine. 5
22. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (isopropylthiomethyl)-pyridine.
- 10 23. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - pivalylthiomethyl-pyridine. 10
24. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - (5 - carbomethoxyethylthio-methyl) - pyridine.
25. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - (β - acetoxyethylthio-methyl)-pyridine.
- 15 26. 2 - Methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - methylthiomethyl-pyridinium methyl iodide. 15
27. Process for the preparation of compounds of the general formula given in claim 1, wherein in a compound of the general formula: —



- 20 in which 20
- R^5 and R^6 , which may be the same or different, are free or functionally changed hydroxyl groups; and
- R^1 and R^2 have the same meanings as in claim 1 and whereby the radical R^2 can contain at least one undesirably functionally changed hydroxyl and/or amino group; with the proviso that at least one of the substituents
- 25 R^5 and R^6 is a functionally changed hydroxyl group, or in a salt thereof, the functionally changed hydroxyl groups and functionally changed amino groups, when present, are converted into free groups. 25
28. Process for the preparation of compounds of the general formula given in claim 1, wherein a 5-thiomethyl-pyridine derivative of the general formula: — 30



- in which
- R^5 and R^6 have the same meanings as in claim 27, and
- 35 X is a hydrogen atom or an alkali metal or alkaline earth metal cation or an unsubstituted or substituted undesired alkyl, aryl or aralkyl radical or is an unsaturated aliphatic hydrocarbon radical or an undesired acyl radical or a radical of the general formula: — 35



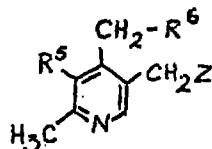
- in which
- 40 R^8 is a $-\text{CH}_2-$ or $-\text{S} \cdot \text{CH}_2-$ group, or a salt thereof, is reacted with an alkylation or acylation agent. 40
29. Process for the preparation of compounds of the general formula given in claim 1, wherein a pyridine derivative of the general formula: —

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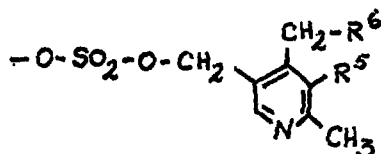
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in which

Z is a sulphonic acid residue, or a halogen atom, or a radical of the general formula: —

5



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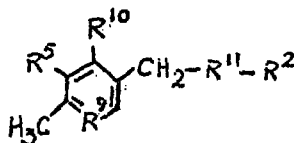
in which

10

R⁵ and R⁶ have the same meanings as in claim 27, or a salt thereof, is reacted with a mercapto compound of the general formula YS.R², in which Y is a hydrogen atom or an alkali metal or alkaline earth metal cation and R² has the same meaning as in claim 1.

10

30. Process for the preparation of compounds of the general formula given in claim 1, wherein a pyridine derivative of the general formula: —



in which

15

R⁹ is an $\text{N}=\text{N}$ or NO group,
R¹⁰ is a —CH₂R⁶ group or a free or functionally changed formyl group, and
R¹¹ is a sulphur atom or an —SO— or —SO₂— group, with the proviso that R⁹

15

is always NO when R¹⁰ is —CH₂R⁶ and R¹¹ is a sulphur atom and that R¹⁰ is always a free or functionally changed formyl group when R⁹ is $\text{N}=\text{N}$ and R¹¹ is a sulphur atom and that R¹¹ is always a —SO— or —SO₂— group when R⁹ is $\text{N}=\text{N}$ and R¹⁰ is —CH₂R⁶,

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R² has the same meaning as in claim 1, and

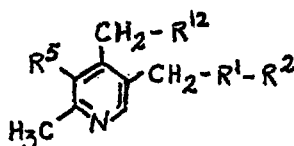
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R⁵ and R⁶ have the same meanings as in claim 27, whereby in the radical R² there can additionally be present undesired substituents which can be split off by reduction or can be converted into desired substituents as defined in claim 1 in connection with the definition of R², or a salt thereof, is treated with a reducing agent and, if necessary, also with a nucleophilic reagent.

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31. Process for the preparation of compounds of the general formula given in claim 1, wherein a pyridoxamine derivative of the general formula: —

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in which

R¹² is an amino group which can be substituted by acyl or by a triphenylmethyl radical,



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29

R^1 and R^2 have the same meanings as in claim 1, and

R^3 has the same meaning as in claim 27, or a salt thereof, the amino substituent R^{12} is converted into a hydroxyl group by treatment with nitrous acid.

5 32. Process for the preparation of compounds of the general formula given in claim 1, wherein a 5-thiomethyl-pyridine derivative of the general formula given in claim 28, in which X is a hydrogen atom or an alkali metal or alkaline earth metal cation, is added to an alkene or alkyne which can be substituted by at least one member selected from halogen, hydroxyl, C_1-C_3 alkoxy, mercapto, C_1-C_3 alkylthio and optionally functionally changed carboxyl and/or $-NR^3R^4$, in which R^3 and R^4 have the same meanings as in claim 1. 10

33. Process for the preparation of compounds of the general formula given in claim 1, wherein in a compound of the general formula given in claim 1 or in a salt thereof in which, however, the radical R^2 contains undesired substituents, especially halogen, CO, NO_2 , NO and/or COOH and/or carbon-carbon multiple bonds or in which desired substituents, especially NH_2 , $N(CH_3)_2$, COOH, SH and/or OH and/or desired carbon-carbon multiple bonds are not yet present, the undesired substituents are split off or converted into desired substituents and/or undesired carbon-carbon multiple bonds are hydrogenated or the desired substituents and/or carbon-carbon multiple bonds are introduced. 15

34. Process according to any of claims 28—33, wherein protective groups still present in substituents R^3 and R^4 are subsequently removed by the method according to claim 27. 20

35. Process according to any of claims 27—34, wherein, when R^1 in the product obtained is a sulphur atom, this is oxidised to give the corresponding compound in which R^1 is a $-SO-$ group. 25

36. Process according to any of claims 27—35, wherein, when the product is obtained in the form of a free base, this is converted into an acid-addition salt or into a quaternary ammonium salt or into a tertiary sulphonium salt.

37. Process according to any of claims 27—35, wherein, when the product is obtained in the form of an acid-addition salt, quaternary ammonium salt or tertiary sulphonium salt, this is converted into the free base. 30

38. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

39. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 27—38. 35

40. Pharmaceutical compositions containing at least one compound according to claim 1, in admixture with a pharmaceutical carrier or adjuvant.

41. Pharmaceutical compositions according to claim 40, whenever in the form of a dosage unit containing 0.1 to 100 mg. of at least one compound according to claim 1. 40

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