

PATENT SPECIFICATION

NO DRAWINGS

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1.153.555



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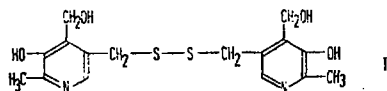
Int. Cl.: —C 07 d 31/24

COMPLETE SPECIFICATION

Preparation of a Sulphur-Containing Pyridine Derivative

We, E. MERCK AKTIENGESELLSCHAFT, a German Body Corporate of Frankfurterstrasse 250, Darmstadt, 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 a process for the preparation of the sulphur-containing pyridine derivative of formula I:



and its salts.

Compound I is known as a therapeutic substance for treating cerebral involution processes, states of nervous exhaustion due to senile involution, arrested development in childhood and other cerebral insufficiencies.

There are several known methods for preparing the disulphide I:

According to German Patents No. 1,135,460 and 1,197,455, the compound can be prepared by reacting a salt of 4,5-bis-bromomethyl - 3 - hydroxy - 2 - methyl - pyridine with an alkali metal xanthate and then treating the product with a base or by reacting said salt with an inorganic disulphide. In another known process (German Patents No. 1,222,052 and 1,227,908) the disulphide I is obtained by the oxidation of 2 - methyl - 3 - hydroxy - 4 - hydroxy - methyl-5-mercaptopmethyl-pyridine or by reacting the corresponding 5-halogen methyl compound with a disulphide (the hydroxy groups in the starting materials are protected, for example by acyl groups) and then

splitting off the protective groups. In another known process, compound I is prepared by treating 5 - chloromethyl - 3 - hydroxy - 4 - hydroxymethyl - 2 - methyl - pyridine with thiourea, an alkali and an oxidising agent (Spanish Patent No. 305,156). According to a Japanese publication, the disulphide I can also be obtained by treating 3-hydroxy-4-hydroxy - methyl - 2 - methyl - 5 - thio - cyanomethyl-pyridine with an alkali or by the action of thiourea, potassium iodide or ammonium thiocyanate on 2 - methyl - 3 - hydroxy - 4 - hydroxymethyl - 5 - thio - sulphatomethyl-pyridine in acid solution (Vitamines [Kyoto], Vol. 30, No. 6, page 431 (1964)). Japanese Patent Publication No. 19067/1966 also discloses a process in which compound I is prepared from 2-methyl-3-hydroxy - 4 - hydroxymethyl - 5 - thiosulphato-methyl-pyridine by reaction with an alkali metal hydrogen sulphide or a lower alkyl mercaptan salt.

Only a few of the known processes for preparing the disulphide I are suitable in practice, since most of them give low yields and a final product that is very difficult to purify; the main disadvantage of most known processes is that the final product is impure. As the disulphide I is used as the active substance in pharmaceutical compositions, it is essential to manufacture a pure compound which is as free as possible from toxic by-products. Another disadvantage of most known methods is that very bad smells are produced by the use of sulphides or mercaptan salts, especially when working in acid solution (e.g. in the method according to Japanese Patent Publication No. 19067/1966).

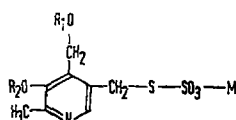
We have now developed an improved process for the preparation of compound I and its salts, which process is well suited for operation on a commercial scale and which

[Price 4s. 6d.]

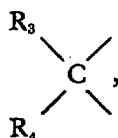
Individual letters e.g. "n.p." should be shown in italics throughout.

gives good yields of the desired products in a pure form.

5. According to the present invention, therefore, we provide a process for the preparation of compound I and its salts, which comprises treating a compound of the formula:



- 10 in which R_1 and R_2 , which may be the same or different, are hydrogen or acyl groups or together form the divalent radical



- 15 R_3 and R_4 , which may be the same or different, are hydrogen or alkyl groups containing up to 5 carbon atoms or together form a alkylidene group containing up to 5 carbon atoms or, together with the carbon atom to which they are attached, form a 5- or 6-membered hydrocarbon ring, and

- 20 M is an alkali metal, preferably sodium or potassium, with an acidic medium and then adjusting the reaction mixture to a neutral, weakly acid or weakly alkaline pH and, if desired, converting the product of formula I obtained to an acid addition for quaternary ammonium salt thereof.

- 25 It is an unexpected discovery that disulphide I can be prepared from Bunte salt II by simple treatment with acid. It has been stated in the literature that a Bunte salt does not give a disulphide when treated with acids (cf. *Journ.Chem.Soc.* 1962, page 2172, last paragraph). It could not therefore have been anticipated that high yields of pure disulphide I can be prepared by the process according to the present invention.

- 30 In the starting material II used in the process according to the invention, the radicals R_1 and R_2 are hydrogen or acyl groups, particularly acyl groups containing up to 4 carbon atoms, such as formyl, acetyl, propionyl and butyryl. R_3 and/or R_4 can be hydrogen or lower alkyl groups with up to 5 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl or butyl, or the radicals R_1 and R_2 together form an alkylidene group, for example methylene, ethylidene, n-propylidene, isopropylidene, butylidene, pentylidene, hexylidene, heptylidene, octylidene or nonylidene. The radicals R_3 and R_4 may also be linked together to form a 5- or 6-membered ring, preferably a cyclopentane or cyclohexane ring. The most preferred starting material II is

that in which R_1 and R_2 are hydrogen and M is sodium. The starting materials II may be prepared, for example, by reacting the corresponding 5-halogen methyl pyridine compounds with an alkali metal thiosulphate. The starting materials do not have to be isolated after being obtained in this way. They can be mixed with an acidic medium while in solution and converted directly by the method according to the invention into compound I or salts thereof.

In the method according to the invention, the acidic medium can be provided by inorganic or organic acids, for example halogen hydric acids, such as hydrochloric, hydrobromic and hydriodic acids, sulphuric acid, phosphoric acid, perchloric acid, or mono- or disulphonic acids, such as benzene and p-toluene sulphonic acids. Acid salts may also be used, for example, Lewis acids, such as zinc chloride or aluminium chloride. Strong mineral acids are preferred, specially halogen hydric acids, hydrochloric acid being the most suitable.

As a rule, it is advisable to use the acidic compound, particularly when an acid is used, in a concentration of from 5 to 20% by weight. The time needed for optimum conversion varies with the acidic compound used and is even more dependent on the temperature. In general, it has been found advantageous to let the acidic compound react with the starting material II for a time varying from 5 minutes to several hours, for example up to 24 hours. At elevated temperatures, for example at reflux temperature, the time required to obtain optimum conversion is shorter than at lower temperatures. It is advantageous to carry out the process at elevated temperatures, more particularly at reflux temperature, in order to speed up the reaction. A high yield of pure product can be obtained, for example, if the starting material II is boiled under reflux for 15 to 45 minutes with dilute hydrochloric acid, more particularly with from 2N to 3N hydrochloric acid. Quantitative conversion can also be obtained, for example, by treating the starting material with about 4N hydrochloric acid at 80°C for 5 hours. At a lower temperature, for example 60°C, high yields can be obtained after approximately 18—20 hours. Hydrobromic acid is preferably used in a concentration of approximately 8% by weight, the reaction being carried out at a fairly high temperature, for example at its boiling point, for approximately 15 to 45 minutes. The most advantageous concentration for sulphuric acid has been found to be from 15 to 25% by weight. p-Toluene sulphonic acid is preferably used in a concentration of approximately 15% by weight, the reaction being carried out, boiling under reflux for approximately 1½ to 3 hours.

The time at which optimum conversion is achieved can be determined by taking samples

materials

with

and titrating with N/10 iodine solution. On completion of the acid treatment, the reaction mixture is adjusted to a slightly acid, neutral or slightly alkaline pH. This may be done, for example, by adding an alkali, such as an alkali metal or alkaline earth metal hydroxide, for example, potassium, sodium or calcium hydroxide, or by using a salt with an alkaline reaction, for example an alkali metal or alkaline earth metal carbonate or bicarbonate, such as sodium, potassium or calcium bicarbonate, or by adding ammonia. The reaction mixture is preferably adjusted to a pH of from 4 to 9 or 10. The product of formula I is thus precipitated and can be separated in conventional manner. If the pH is strongly alkaline, however, the final product partly redissolves. For this reason, the pH is preferably from 4 to 8, and advantageously from 6.5 to 8, in order to encourage precipitation and minimise resolution. If necessary, the product can be further purified by recrystallizing from a suitable solvent, such as n-butanol or dimethyl formamide/water.

If desired, the disulphide I can then be converted by conventional procedures to an acid addition salt or quaternary ammonium salt. Physiologically acceptable acid addition salts may be obtained, for example, by adding inorganic acids, such as hydrochloric, hydrobromic, phosphoric, sulphuric or nitric acids, or organic acids, such as alkyl sulphonic acids, for example, methane sulphonic acid or p-toluene sulphonic acid. These are added to compound I in free base form.

Strong mineral acids are preferred. Quaternary ammonium salts are obtained by reacting the free base I with alkyl halides, particularly methyl or ethyl halides, such as methyl iodide or ethyl bromide. If an undesirable acid addition salt of compound I is formed, the base can be liberated and converted into a different acid addition salt.

In order that the invention may be more fully understood, the following examples are given by way of illustration only:—

EXAMPLE 1

A solution of 124 g sodium thiosulphate in 500 ml water was added, while stirring, to a suspension of 93.5 g 5-chloromethyl-3-hydroxy 4 - hydroxymethyl - 2 - methyl - pyridine in 500 ml of water. The mixture was kept at 60°C for between 1 and 1½ hours and 200 ml concentrated HCl were then added. The mixture was then boiled under reflux for half an hour. After cooling, the pH of the solution was adjusted to 6—7 by the addition of dilute NaOH and the precipitated bis - [3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl] disulphide is filtered off with suction and washed with water and acetone. Yield: 92 g

(=100% of the theoretical); m.p.=222°C (decomposition).

EXAMPLE 2

23.2 g 5 - bromomethyl - 3 - hydroxy - 4 - hydroxymethyl - 2 - methyl - pyridine were suspended in 70 ml water, the suspension was mixed with a solution of 24.8 g sodium thiosulphate in 130 ml of water, and the mixture was kept at 40—45°C for 1½ hours. 50 ml concentrated HCl were then added and the mixture was heated under reflux for half an hour. After cooling, the pH of the solution was adjusted to 6.5 and the precipitated bis - [3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl] disulphide was filtered off with suction. Yield: 17 g; m.p.=220—222°C (decomposition).

EXAMPLE 3

5 g sodium 3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl - thiosulphate were heated under reflux in 50 ml 4N H₂SO₄ for 30 minutes, the mixture was cooled and then neutralised. The precipitated bis - [3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl] disulphide was filtered off with suction. Yield: 2.97 g (=93% of theoretical); m.p.=220—222°C (decomposition).

EXAMPLE 4

10 g sodium 3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl - thiosulphate were boiled under reflux for 30 minutes with 100 ml 2N HBr and the mixture then neutralised. Yield: 4.6 g (=72% of theoretical) of bis - [3 - hydroxy - 4 - hydroxymethyl - 2 - methyl - pyridyl - (5) - methyl] disulphide; m.p.=220—222°C (decomposition).

EXAMPLE 5

5 g sodium 3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl - thiosulphate were boiled for 2 hours under reflux in 50 ml 15% aqueous p-toluene sulphonic acid and the solution was subsequently neutralised. Yield: 2.85 g (=89% of theoretical) of bis - [3 - hydroxy - 4 - hydroxymethyl - 2 - methyl - pyridyl - (5) - methyl] disulphide; m.p.=220—222°C (decomposition).

EXAMPLE 6

6 g sodium 2 - methyl - 3 - acetoxy - 4 - acetoxy - methyl - pyridyl - (5) - methyl - thiosulphate (prepared by reacting the corresponding 5-bromomethyl pyridine compound with sodium thiosulphate) were boiled for half an hour under reflux in 60 ml 2N hydrochloric acid and the mixture was then neutralised with 2N caustic soda. The precipitated bis - [3 - hydroxy - 4 - hydroxy - methyl - 2 - methyl - pyridyl - (5) - methyl] disulphide was filtered off with suction.

recrystallising

Yield: 2.8 g (=85% of the theoretical);
m.p.=220—222°C (decomposition).

EXAMPLE 7

- 24 g sodium thiosulphate were dissolved
5 in 200 ml water, 22.8 g 4',5'-isopropylidene-
3 - chloromethyl - 5 - hydroxyl - 4 -
hydroxymethyl-6-methyl pyridine (m.p.=
100°C) were added and the mixture was
10 stirred at 60°C for 2 hours. 50 Ml concen-
trated hydrochloric acid were added to the
mixture, which was then boiled under reflux
for 30 minutes. After cooling, the pH of the
solution was adjusted to 6—7 by the addition
15 of dilute caustic soda and the precipitated
bis - [3 - hydroxy - 4 - hydroxymethyl - 2 -
methyl - pyridyl - (5) - methyl] disulphide
was filtered off with suction. Yield: 17.3 g;
m.p.=220—222°C (decomposition).

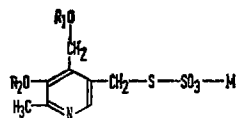
EXAMPLE 8

- 5.35 g 4',5' - cyclohexylidene - 3 - chloro -
20 methyl - 5 - hydroxy - 4 - hydroxymethyl -
6-methyl-pyridine were suspended in 50 ml
water, 4.5 g sodium thiosulphate were added
and the mixture was stirred at 60°C for 3
25 hours. 10 Ml concentrated hydrochloric acid
were then added and the mixture was heated
under reflux for 30 minutes. After cooling,
the acid solution was extracted with ether so
as to remove the liberated cyclohexanone.
30 The solution was neutralised by the addition
of dilute caustic soda and the precipitated
bis - [3 - hydroxy - 4 - hydroxymethyl - 2 -
methyl pyridyl - (5) - methyl] disulphide
was filtered off with suction. Yield: 3.1 g;
35 m.p. 220—222°C (decomposition).

WHAT WE CLAIM IS:—

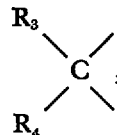
1. A process for the preparation of compound I herein and its salts, which comprises treating a compound of the formula:

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II

in which R_1 and R_2 , which may be the same or different, are hydrogen or acyl groups or together form the divalent radical



R_3 and R_4 , which may be the same or different, are hydrogen or alkyl groups containing up to 5 carbon atoms or together form a alkylidene group containing up to 5 carbon atoms or, together with the carbon atoms to which they are attached, form a 5- or 6-
45 50

M is an ~~acidic~~ metal, with an acidic medium and then adjusting the reaction mixture to a neutral, weakly acidic or weakly alkaline pH and, if desired, converting the product of formula I obtained to an acid addition or quaternary ammonium salt thereof.
55

2. A process according to claim 1, in which the acidic medium is a dilute solution of a strong mineral acid.
60

3. A process according to claim 1 or 2, in which the acidic medium is 1N to 4N hydrochloric acid.

4. A process according to any of claims 1 to 3, in which the reaction mixture is adjusted to a pH of from 6.5 to 8.
65

5. A process for the preparation of compound I herein substantially as herein described in any of the Examples.
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6. Compound I herein and its acid addition and quaternary ammonium salts when prepared by the process claimed in any of claims 1 to 5.

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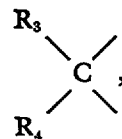
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Yield: 2.8 g (=85% of the theoretical);
m.p.=220—222°C (decomposition).

in which R_1 and R_2 , which may be the same or different, are hydrogen or acyl groups or together form the divalent radical



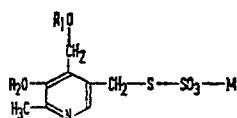
- EXAMPLE 7
- 24 g sodium thiosulphate were dissolved in 200 ml water, 22.8 g 4',5'-isopropylidene-3-chloromethyl-5-hydroxyl-4-hydroxymethyl-6-methyl pyridine (m.p.=100°C) were added and the mixture was stirred at 60°C for 2 hours. 50 Ml concentrated hydrochloric acid were added to the mixture, which was then boiled under reflux for 30 minutes. After cooling, the pH of the solution was adjusted to 6—7 by the addition of dilute caustic soda and the precipitated bis-[3-hydroxy-4-hydroxymethyl-2-methyl-pyridyl-(5)-methyl] disulphide was filtered off with suction. Yield: 17.3 g; m.p.=220—222°C (decomposition).

- EXAMPLE 8
- 5.35 g 4',5'-cyclohexylidene-3-chloromethyl-5-hydroxy-4-hydroxymethyl-6-methyl-pyridine were suspended in 50 ml water, 4.5 g sodium thiosulphate were added and the mixture was stirred at 60°C for 3 hours. 10 Ml concentrated hydrochloric acid were then added and the mixture was heated under reflux for 30 minutes. After cooling, the acid solution was extracted with ether so as to remove the liberated cyclohexanone. The solution was neutralised by the addition of dilute caustic soda and the precipitated bis-[3-hydroxy-4-hydroxymethyl-2-methyl-pyridyl-(5)-methyl] disulphide was filtered off with suction. Yield: 3.1 g; m.p. 220—222°C (decomposition).

WHAT WE CLAIM IS:—

1. A process for the preparation of compound I herein and its salts, which comprises treating a compound of the formula:

40



R_3 and R_4 , which may be the same or different, are hydrogen or alkyl groups containing up to 5 carbon atoms or together form an alkylidene group containing up to 5 carbon atoms or, together with the carbon atoms to which they are attached, form a 5- or 6-membered hydrocarbon ring, and

M is an ~~acidic~~ metal, with an acidic medium and then adjusting the reaction mixture to a neutral, weakly acidic or weakly alkaline pH and, if desired, converting the product of formula I obtained to an acid addition or quaternary ammonium salt thereof.

2. A process according to claim 1, in which the acidic medium is a dilute solution of a strong mineral acid.

3. A process according to claim 1 or 2, in which the acidic medium is 1N to 4N hydrochloric acid.

4. A process according to any of claims 1 to 3, in which the reaction mixture is adjusted to a pH of from 6.5 to 8.

5. A process for the preparation of compound I herein substantially as herein described in any of the Examples.

6. Compound I herein and its acid addition and quaternary ammonium salts when prepared by the process claimed in any of claims 1 to 5.

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