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PATENT SPECIFICATION

NO DRAWINGS

833,391

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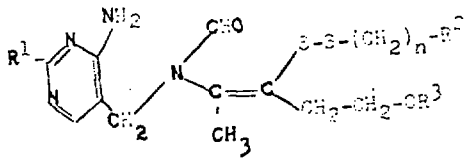
International Classification:—C07d.

COMPLETE SPECIFICATION

Derivatives of Thiamine and their production

We, TAKEDA PHARMACEUTICAL INDUSTRIES, LTD., of 27, 2-chome, Doshomachi, Higashi-ku, Osaka, Japan, a Company organized under the Laws of Japan, 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;—

This invention relates to derivatives of thiamine and their production and more particularly to novel compounds having the general formula:



wherein R^1 is a methyl or ethyl radical, R^2 is a tetrahydrofuryl or tetrahydropyranyl radical, R^3 is a hydrogen or an acyl radical, and n is a positive whole number, from 1 to 3, and to a process for producing the same.

In recent years many kinds of thiamine derivatives having asymmetrical structures resembling the above formula have become known but all such derivatives have an alkyl, aryl, aralkyl or the like radical in place of the $-(CH_2)_n-R^2$ group. These compounds are superior to thiamine acid salts in medicinal effect, but they generally have an unpleasant mercaptan-like odour.

The inventors of the present invention have sought to make new and better disulphide-type thiamine derivatives and have succeeded in obtaining a new group of disulphide-type thiamine derivatives which do not have the above mentioned drawback and the medicinal effect of which is superior to that of known derivatives, not to speak of that of thiamine acid salts. The superiority of the compounds of this invention is evident for example from the results of the following tests:—

In the tests were used three different thiamine derivatives belonging to the new group, i.e. thiamine tetrahydrofurfuryl disulphide, thiamine tetrahydrofuryl - 2 - propyl disulphide and thiamine tetrahydropyranyl - 2 - methyl disulphide (referred to as TTFD, TTPD and TTMD, respectively), which are representable by the afore-mentioned general formula wherein:

TTFD: $R^1=CH_3$, R^2=furyl, $R^3=H$, $n=1$

TTPD: $R^1=CH_3$, R^2=furyl, $R^3=H$, $n=3$

TTMD: $R^1=CH_3$, R^2=pyranyl, $R^3=H$, $n=1$

Control tests were conducted using thiamine propyl disulphide, which is the most effective of all known disulphide-type derivatives, and thiamine hydrochloride.

When TTFD, TTPD or TTMD is injected intravenously into ears of rabbits, the thiamine concentration in their blood is increased remarkably and the high concentration is maintained for a long time. The tests were conducted with rabbits weighing about 2 kg. each. The amount of each sample injected corresponds to 10 mg. of thiamine hydrochloride, i.e. 11.8 mg. of TTFD, 13.7 mg. of TTPD, 12.3 mg. of TTMD and 10.6 mg. of thiamine propyl disulphide. The thiamine concentration in the blood was measured several times after the injection. The results were as follows:

Sample	Cases	Thiamine in blood (mean value)*					
		before injection	after injection				
			3 min.	10 min.	30 min.	60 min.	90 min.
TTFD 11.8 Mg.	4	34.8	2335	2311	2178	1882	1756
TTPD 13.7 mg.	8	42.8	1529	1729	1595	1463	1282
TTMD 12.3 mg.	8	48.0	2372	2471	2227	1924	1818
Thiamine propyl- disulphide 10.6 mg.	5	63.4	1648	1564	1459	1338	1229
Thiamine hydro- chloride 10.0 mg.	1	46.7	718	516	282	156	140

* Thiamine in blood is the concentration of total thiamine in 1 ml of whole blood expressed as thousandths of 1%.

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In the above tests the quantitative determination of the thiamine in blood was conducted by a chemical method, i.e. the thiamine in blood was reduced with cystein and then determined by the thiochrome method using bromocyanide.

From the results of the above tests, it is obvious that when the compounds of this invention are injected into living bodies, the concentration of the total thiamine in blood becomes far higher than that in the case of thiamine hydrochloride or thiamine propyl disulphate and the durability of the high concentration is also far longer than in the case of the above two compounds.

In another test TTFD was administered *per os* or by intra - peritoneal injection to rats, and its lethal dose was observed. As a result, it was found that the LD_{50} value (mg./kg.) was very low, as shown below.

Administration conditions	TTFD	Thiamine hydrochloride
orally	2200	9000
intraperitoneal injection	540	500

The compounds of the present invention may be prepared by a process which comprises subjecting thiamine, ethyl thiamine (a compound having the same structure as thiamine except that the methyl group in the pyrimidine nucleus is replaced by an ethyl radical) or one of their O-acyl derivatives (these compounds will hereinafter be referred to as "thiamine or its related compounds") to reaction with an active compound which is able to convert the —SH group into the

$$—S—S—(CH_2)_n—R^2$$

group, in which group R^2 is a furyl or pyranyl radical and n is a positive whole number from 1 to 3.

Thiamine or its related compounds are generally available as acid salts such as the hydrochloride, nitrate and sulphate and these acid salts are all usable in the present invention. As the active compound for introducing the

$$—S—S—(CH_2)_n—R^2$$

group into the starting material there may be used compounds having the general formulae:

$$R^2—(CH_2)_n—S—SO_3M$$

$$R^2—(CH_2)_n—\underset{\diagup\ \diagdown}{\overset{O}{S}}—S—R$$

$$R^2—(CH_2)_n—\underset{\diagup\ \diagdown}{\overset{O_2}{S}}—S—R$$

$$R^2—(CH_2)_n—S—S—CN$$

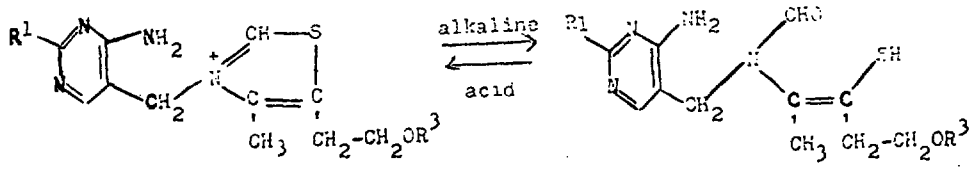
$$R^2—(CH_2)_n—S—X$$

$$R^2—(CH_2)_n—SH$$

in which compounds R^2 and n have the aforementioned significances, M is an alkali metal or alkaline earth metal, R is an alkyl radical or a group similar to R^2, and X is a halogen atom.

In the process of the present invention one of the above compounds is reacted with a thiol type thiamine or related compound.

It is generally known that thiamine and its related compounds exist in solution in a state of equilibrium between the ammonium-type and the thiol-type, and that the equilibrium shifts to the thiol-type in alkaline conditions and to the ammonium - type in acid conditions as shown below:



Accordingly, the reaction of the present invention takes place in neutral or alkaline conditions or in other word the reaction proceeds smoothly at a non-acidic pH. The yield of the product may be lowered when the reaction is conducted in a medium which is too strongly alkaline, because not only the thiamine or its related compounds but also the product may be decomposed under such conditions. The most preferable pH lies between 7 and 9.

The reaction is carried out in a solvent such as water, an alcohol, acetone, an acetic ester or a mixture of such solvents, but other solvents may be used if they are inert to the reaction system. Although most of the above-exemplified reagents for use in introducing the

$$—S—(CH_2)_n—R^2$$

groups are used without the aid of any other reagent, the

$$R^2—(CH_2)_n—SH$$

type reagent alone is employed together with an oxidising agent such as bromine, hydrogen peroxide, potassium permanganate or an alkali bichromate. Electrolytic oxidation may also be applied for the purpose.

The invention is not however, limited to the use of the particular process mentioned above for converting the —SH group or thiol-type

thiamine or its related compound into the

$$-S-S-(CH_2)_n-R^2$$

group.

When the starting material is an O-acyl derivative of thiamine or of ethyl thiamine, the product is also the corresponding O-acyl derivative, but the acyl group can readily be split off by a conventional method. If the starting material has a free hydroxyl radical, the product also has a free hydroxyl radical, but the hydroxyl group of the product can be acylated in a usual manner, if necessary.

The following Examples further illustrate and explain the actual working of the process of this invention; in all the Examples parts are by weight, analytical values are in per cent, and all temperatures are uncorrected.

EXAMPLE 1.

To a solution of 20 parts of thiamine hydrochloride in 30 parts of water is added an aqueous solution of sodium hydroxide (7.2 parts of NaOH in 30 parts of water), and the mixture is cooled with water. The mixture is allowed to stand for 30 minutes, 60 parts of chloroform is added, followed by a solution of 30 parts of crude sodium tetrahydrofurfuryl-thiosulphate in 30 parts of water, and the whole is stirred for 30 minutes. The chloroform layer is separated and the aqueous layer is extracted twice with 20 parts of chloroform. All the chloroform solutions are combined and shaken with 50 parts of 5% hydrochloric acid. The acid solution is decolourised and neutralised with alkali metal carbonate, whereupon thiamine tetrahydrofurfuryl disulphide separates out in the resinous state but soon solidifies (m.p. 129° C. (decomp.)). The yield is 16 parts. Recrystallisation from ethyl acetate gives colourless prisms melting at 132° C. (decomp.).

Analysis:

Calcd. for $C_{17}H_{26}O_3N_4S_2$: C, 51.22; H, 6.58.
Found : C, 51.11; H, 6.45.

EXAMPLE 2.

To 100 parts of 50% ethanol are added 3 parts of tetrahydrofurfuryl tetrahydrofurfurylthiosulphinate and 2 parts of thiamine hydrochloride and the mixture is adjusted to pH 8 with a 10% aqueous solution of sodium hydroxide. While maintaining the pH, the mixture is warmed for one hour at a temperature between 50—60° C., when the thiochrome reaction of the mixture becomes negative. After decolourising, the mixture is concentrated to dryness under reduced pressure and a little amount of water is added to the residue to dissolve inorganic impurities, when an oily substance remains, which, however, solidifies when the wall of the flask is scratched (m.p. 129° C. (decomp.)). The yield is 1.2 parts. Recrystallisation from ethyl acetate gives colourless prisms, m.p. 132° C. (decomp.). No depression of melting point is observed when the product is melted with the product of Example 1.

EXAMPLE 3.

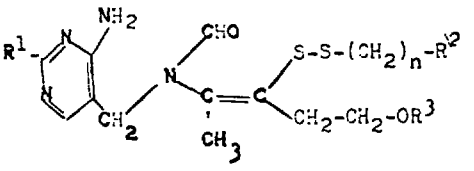
To a solution of 3.4 parts of thiamine hydrochloride in 5 parts of water is added a solution of 1.2 parts of sodium hydroxide in 5 parts of water and the mixture is left standing for 30 minutes. To the mixture is then added 12 parts of chloroform, followed by a solution of 4.7 parts of sodium tetrahydrofuryl - 2 - propyl thiosulphate in 5 parts of water with stirring. Thirty minutes later, the chloroform layer is separated and the aqueous layer is extracted with 12 parts of chloroform. The chloroform solutions are combined and shaken with 25 parts of 5% hydrochloric acid, and the acid solution, after being decolourised, is neutralised with alkali metal carbonate, when thiamine tetrahydrofuryl - 2 - propyl disulphide separates out in the resinous state. The yield is 3 parts.

EXAMPLE 4.

To a solution of 3.4 parts of thiamine hydrochloride in 5 parts of water is added a solution of 1.2 parts of sodium hydroxide in 5 parts of water. The mixture is allowed to stand for 30 minutes and 12 parts of chloroform is added, followed by 6 parts of crude sodium tetrahydropyran - 2 - methyl thiosulphate with stirring. After 30 minutes, the chloroform layer is separated and the aqueous layer is extracted with 12 parts of chloroform. The chloroform solutions are combined and shaken with 15 parts of 5% hydrochloric acid. The acid solution is decolourised and neutralised with alkali metal carbonate, whereupon thiamine tetrahydropyran - 2 - methyl disulphide separates out as a resinous substance which, however soon crystallises in colourless prisms, m.p. 126—127° C. (decomp.). The yield is 1.4 parts. Recrystallisation from benzene gives large colourless leaves.

WHAT WE CLAIM IS:—

1. Compounds having the formula



wherein R^1 is a methyl or ethyl group, R^2 is a tetrahydrofuryl or tetrahydropyranyl group, R^3 is hydrogen or an acyl group and n is a positive whole number from 1 to 3.

2. Compounds having the formula

* C L M S *

thiamine or its related compound into the $-S-S-(CH_2)_n-R^2$ group.

When the starting material is an O-acyl derivative of thiamine or of ethyl thiamine, the product is also the corresponding O-acyl derivative, but the acyl group can readily be split off by a conventional method. If the starting material has a free hydroxyl radical, the product also has a free hydroxyl radical, but the hydroxyl group of the product can be acylated in a usual manner, if necessary.

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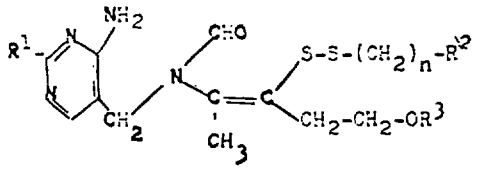
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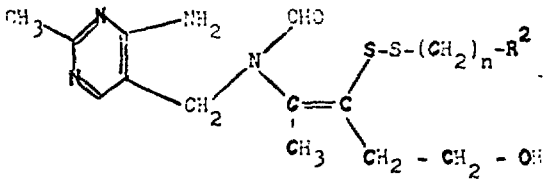


wherein R^1 is a methyl or ethyl group, R^2 is a tetrahydrofuryl or tetrahydropyranyl group, R^3 is hydrogen or an acyl group and n is a positive whole number from 1 to 3.

2. Compounds having the formula

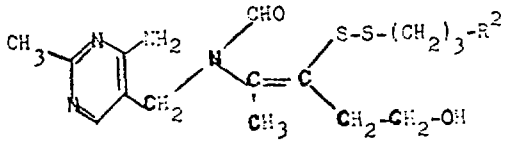
* C L M S *

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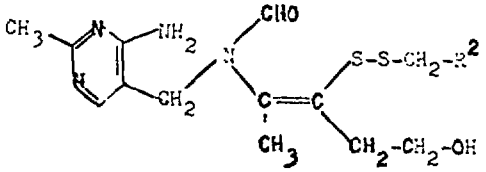
wherein R^2 is a tetrahydrofuryl or tetrahydropyranyl group and n is a positive whole number from 1 to 3.

3. Compounds having the formula



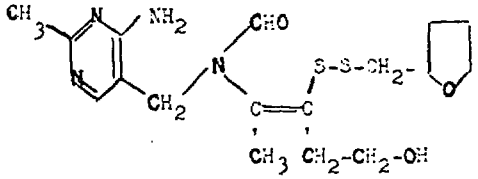
wherein R^2 is a tetrahydrofuryl or tetrahydropyranyl radical.

4. Compounds having the formula

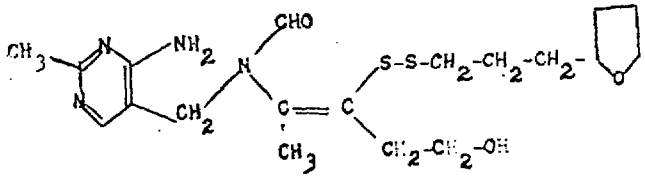


wherein R^2 is a tetrahydrofuryl or tetrahydropyranyl radical.

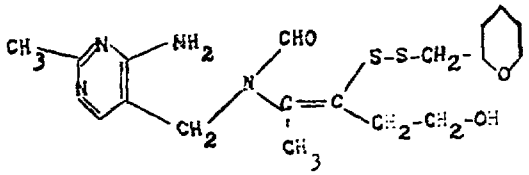
5. The compound having the formula



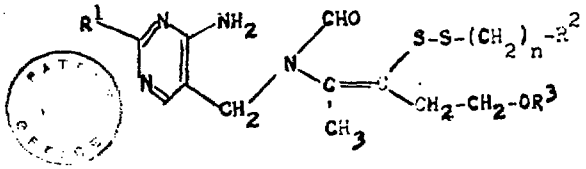
6. The compound having the formula



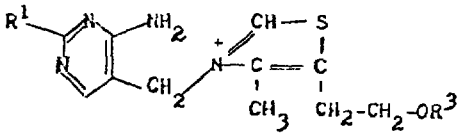
7. The compound having the formula



8. A process for producing a compound having the formula



wherein R is a methyl or ethyl radical, R^2 is a tetrahydrofuryl or tetrahydropyranyl group, R^3 is hydrogen or an acyl group and n is a positive whole number from 1 to 3, which comprises reacting a compound having the formula



where R^1 and R^3 have the aforementioned significance with a reagent which serves to convert the —SH group into a group of the formula

$$—S—S—(CH_2)_n—R^2$$

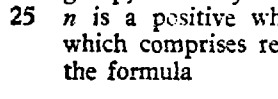
wherein R^2 and n have the aforementioned significances.

9. A process as claimed in claim 8, wherein the reagent which serves to convert the —SH group into a group of the formula

$$—S—S—(CH_2)_n—R^2$$

is of the formula

$$R^2—(CH_2)_n—S—SO_3—M,$$



* C L M S *

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$$R^2—(CH_2)_n—\underset{\diagdown\,O_2\,\diagup}{S}—S—R,$$

$$R^2—(CH_2)_n—S—S—CN,$$

or

$$R^2—(CH_2)_n—S—X,$$

or is

$$R^2—(CH_2)_n—SH$$

plus an oxidising agent or electrolytic oxidation, in which formula R is an alkyl radical or a group similar to R^2, X is a halogen atom and M is an alkali metal or alkaline earth metal.

10. Processes as claimed in claim 8, substantially as hereinbefore described.

11. Compounds as claimed in claim 1, whenever prepared by a process as claimed in any of claims 8 to 10.

ELKINGTON AND FIFE,
Consulting Chemists and Chartered Patent Agents,
Bank Chambers, 329, High Holborn, London, W.C.1,
Agents for the Applicants.

ERRATA

SPECIFICATION No. 833,391

Page 4, line 106, *for* "have" *read* "having"
Page 5, line 22, *for* "RZ" *read* "R¹"

THE PATENT OFFICE
12th July, 1960