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PATENT SPECIFICATION

NO DRAWINGS

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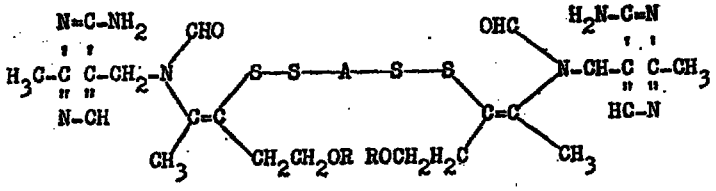
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Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

New Thiamine Derivatives and the preparation thereof

We, TAKEDA CHEMICAL INDUSTRIES LTD. of 27, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a body corporate organised 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 new disulphide-type thiamine derivatives and to a process for the preparation thereof. The present invention provides alkylene bis-thiamine disulphides of the general formula:



(I)

in which A is a saturated or unsaturated alkylene group containing from 4 to 20 carbon atoms, and R is a hydrogen atom, a carboxylic acid acyl group, an alkoxycarbonyl group containing up to 7 carbon atoms or a phosphono group.

Many kinds of thiamine derivatives which have a superior medicinal effect to thiamine acid salts are known. Of these thiamine derivatives, thiamine alkyl disulphides, e.g. thiamine propyl disulphide, have been used medicinally as the best such derivative. However, these compounds have the drawback of having an unpleasant mercaptan-like odour and bitter taste.

Therefore much research has been carried out to try to find new thiamine derivatives which do not have this unpleasant mercaptan-like odour. This research lead to the discovery of thiamine tetrahydrofurfuryl disulphide which has a substantially equivalent medicinal effect compound with thiamine propyl disulphide. Although thiamine tetrahydrofurfuryl disulphide was odourless, it has a disadvantageous bitter taste. These unavoidable deficiencies considerably restrict the use of the known thiamine derivatives.

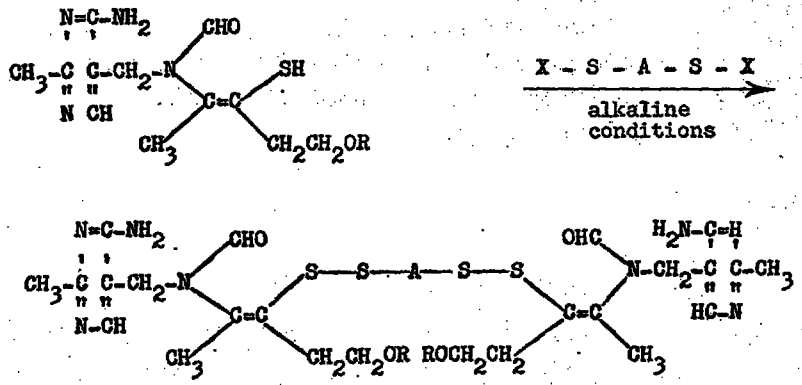
We have now found new thiamine derivatives of the general formula (I) above, which are at least as good medicinally as thiamine propyl disulphide or thiamine tetrahydrofurfuryl disulphide and furthermore which do not have an unpleasant odour or a bitter taste.

The thiamine derivatives of general formula (I), i.e. alkylene bisthiamine disulphide and its O-esters, are prepared by reacting thiamine or an O-ester thereof with an alkylene dithiol derivative of the general formula (II):

$$X—S—A—S—X \qquad (II)$$

wherein A has the same meaning as defined above, X represents $—SO_3M$, $—SO_2—R^1$, $—SO—R^1$, —S—CN, or a halogen, M is an alkali metal or one valency of an alkaline

earth metal and R^1 is a hydrocarbon residue having up to seven carbon atoms. The reaction may be expressed by the following reaction diagram:



Examples of alkylene dithiol derivatives of formula (II) are alkali metal or alkaline earth metal alkylene bisthiosulphates (MSO_3—S—A—S—SO_3M, for example sodium alkylene bisthiosulphates, potassium alkylene bisthiosulphates or calcium alkylene bisthiosulphates), alkylene bisthiosulphonates (R^1SO_2—S—A—S—SO_2R^1, e.g. alkylene bismethanesulphonates, alkylene bisethanesulphonates or alkylene bisbenzenesulphonates), alkylene bisthiosulphinates (R^1SO—S—A—S—SOR^1, e.g. alkylene bismethanesulphinates, alkylene bisethanesulphinates or alkylene bisbenzensulphinates), alkylene bis-thiothiocyanates (NC—S—S—A—S—S—Cn), or alkylene bissulphenylhalides (e.g. alkylene bissulphenyl chlorides or alkylene bissulphenyl bromides).

The alkylene group A comprises a polymethylene group containing 4 to 20, preferably 6 to 10 carbon atoms, and possibly one or more unsaturated linkages e.g. a double bond. Examples of such groups are:

tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, dodecamethylene tetradecamethylene, hexadecamethylene, octadecamethylene, oct-2-enylene, hept-2-enylene, hept-, 4-dienylene and hex-2-enylene radicals.

The preparation of the new compounds is carried out in an aqueous medium while maintaining the pH of the reaction system alkaline at least at a non-acidic pH. Reagents which can be used to adjust the reaction system to an alkaline pH are, for example, inorganic bases e.g. sodium hydroxide, potassium hydroxide and ammonia, and organic bases e.g. pyridine and aniline.

O-esters of thiamine which may be used as one of the starting materials, can be any thiamine esters formed with carboxylic acid containing up to seven carbon atoms, with carbonic acid mono-alkyl esters containing up to seven carbon atoms, or with phosphoric acid. Preferably, the thiamine esters are, for example, formic acid ester, acetic acid ester, propionic acid ester, benzoic acid ester, monoethyl carbonic acid ester, monomethyl carbonic acid ester and phosphoric acid ester.

Alternatively, if the compound of general formula (I) prepared is one in which R is a hydrogen atom, it may be converted into the corresponding O-ester, such as formate, acetate, propionate, methoxycarbonate, ethoxycarbonate, benzoate or phosphate, by esterification by means known *per se*. To carry out such an esterification, the esterifying agent may be also acid anhydride or acid halide of the carboxylic acid to be introduced. The reaction is preferably carried out in basic organic solvent such as pyridine, dimethylaniline or mixtures thereof, with or without using an inert solvent such as dimethylformamide or dioxane. The esterification may also be effected by using the desired carboxylic acid and its anhydride with or without using a dehydrating agent.

The novel compounds of formula (I) are absorbed better from intestines, transferred to the blood and various internal organs at a high thiamine level, and the toxicities are very low. Furthermore, the compounds have neither an unpleasant odour nor a bitter taste. They can be administered in the usual manner, in admixture with a pharmaceutical diluent or carrier.

The following Examples illustrate the invention, the temperatures all being uncorrected.

EXAMPLE 1

A solution of 3 grams of decamethylene - 1,10 - dibromide and 5 grams of sodium thiosulphate in 60 c.c. of 50% aqueous ethanol was stirred, while heating at 75°C. on a water bath for 3 hours. Evaporation of the solvent gave sodium decamethylene-1,10-bisthiosulphate.

25 grams of sodium hydroxide dissolved in 15 cubic centimetres of water were added to a solution of 6.7 grams of thiamine chloride hydrochloride in 20 cubic centimeters of water. After standing for 30 minutes, sodium decamethylene-1,10-bisthiosulphate was added and a yellow oily substance, was formed. The oily substance was extracted with chloroform. The chloroform layer was washed and dried, and then chloroform was distilled off. The residue was mixed with ethyl acetate and left to stand for crystals to separate. Recrystallisation from a mixture of methanol and ethyl acetate gave 4.5 grams of decamethylene-1,10-bis-(thiamine disulphide) as a colourless powder melting at 139—140°C.

EXAMPLE 2

A solution of 5 grams of sodium thiosulphate in 20 cubic centimetres of water was added to a solution of 2.3 grams of pentamethylene-1,5-dibromide in 20 cubic centimetres of ethanol while stirring and heating under reflux on a water bath. After a further heating for 30 minutes, the solvent was removed to give crude crystals of sodium pentamethylene-1,5-bisthiosulphate. A solution of 2.4 grams of sodium hydroxide in 20 cubic centimetres of water was added to a solution of 6.8 grams of thiamine chloride hydrochloride in 20 cubic centimeters of water. The solution obtained was added while stirring to 10 c.c.s. of a solution of the above obtained sodium pentamethylene-1,5-bisthiosulphate to give a yellow oily substance. The oily substance was extracted with chloroform. After the chloroform layer had been washed with water and dried, chloroform was evaporated to obtain 4.7 grams of pentamethylene-1,5-bis-(thiamine disulphide). Upon recrystallisation from a mixture of chloroform and ethyl acetate, the crystals melted at 77—79°C.

EXAMPLE 3

A solution of 2.7 grams of octamethylene-1,8-dibromide, 5 grams of sodium thiosulphate in 60 cubic centimetres of 50% aqueous ethanol was stirred while heating at 75°C. on water bath for 30 minutes. Evaporation of the solvent gave sodium octamethylene-1,8-bisthiosulphate.

A solution of 2.5 grams of sodium hydroxide in 15 cubic centimetres of water was added to a solution of 6.7 grams of thiamine chloride hydrochloride in 20 cubic centimetres of water. After the resulting solution had stood for 30 minutes, the above obtained sodium octamethylene bisthiosulphate was added thereto to yield a yellow oily substance. The oily substance was extracted with chloroform, the chloroform layer was washed with water and dried, and chloroform was evaporated to give 5 grams of octamethylene-1,8-bis-(thiamine disulphide). Upon recrystallisation from a mixture of methanol and ethyl acetate, the crystals melted at 133—134°C.

EXAMPLE 4

A mixture of 2.4 grams of hexamethylene-1,6-dibromide and 5 grams of sodium thiosulphate in 40 cubic centimetres of 50% aqueous methanol was stirred while heating at 75°C. on a water bath for 30 minutes. Evaporation of the solvent under reduced pressure gave sodium hexamethylene-1,6-bisthiosulphate.

A solution of 2.4 grams of sodium hydroxide in water was added to a solution of 7.4 grams of thiamine chloride hydrochloride in 20 cubic centimetres of water. After standing for 30 minutes, the above-obtained sodium hexamethylene-1,6-bisthiosulphate was added to give a yellow oily substance. The oily substance was extracted with chloroform. After the chloroform layer had been washed with water and dried, and chloroform was evaporated to yield 5.1 grams of hexamethylene-1,6-bis-(thiamine disulphide). Upon recrystallisation from a mixture of chloroform, ethanol and ether, the crystals melted at 132.5—133°C.

EXAMPLE 5

A mixture of 2.5 grams of hept-2-enylene-1,7-dibromide, 5 grams of sodium thiosulphate and 50 cubic centimetres of 50% aqueous methanol was stirred for 30 minutes while heating at 75°C. on water bath. Evaporation of the solvent gave sodium hept-2-enylene-1,7-bisthiosulphate.

A solution of 2.4 grams of sodium hydroxide in 20 cubic centimetres of water was added to a solution of 6.7 grams of thiamine chloride hydrochloride in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes, the above-obtained sodium hept-2-enylene-1,7-bisthiosulphate was added thereto to give a yellow oily substance. The oily substance was extracted with chloroform. After the chloroform

layer had been washed with water and dried, chloroform was evaporated to yield 4.3 grams of hept-2-enylene-1,7-bis-(thiamine disulphide).

EXAMPLE 6

Sodium-hexamethylene-1,6-bisthiosulphate was prepared by the reaction of 2.4 grams of hexamethylene-1,6-dibromide with 5 grams of sodium thiosulphate in the same way as in Example 4.

A solution of 2.4 grams of sodium hydroxide in 20 cubic centimetres of water was added to a solution of 7.6 grams of O-acetylthiamine chloride hydrochloride in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes, the above-obtained sodium hexamethylene-1,6-bisthiosulphate in 10 cubic centimeters of water was added thereto to give a yellow oily substance. The oily substance was extracted with ethyl acetate. After the ethyl acetate layer had been washed with water and dried the ethyl acetate was evaporated. The residue was mixed with water and crystallised to yield 4.7 grams of hexamethylene-1,6-bis-(acetylthiamine disulphide). Upon recrystallisation from ethyl acetate and isopropyl ether, the crystals melted at 106—108°C.

EXAMPLE 7

Sodium hexamethylene-1,6-bisthiosulphate was prepared by the reaction of 1.2 gram of hexamethylene-1,6-dibromide with 2.5 grams of sodium thiosulphate in the same way as in Example 4.

A solution of 5 grams of O-ethoxycarbonylthiamine bromide hydrobromide was dissolved in 10 cubic centimetres of water while stirring. After the resultant solution had stood for 30 minutes, the above-obtained sodium hexamethylene-1,6-bisthiosulphate in 10 cubic centimetres of water was added thereto to give a yellow oily substance. Thereafter, the oily substance was treated in the same way as in the preceding Examples to obtain 1.2 grams of hexamethylene-1,6-bis(ethoxycarbonylthiamine disulphide) melting at 77—80°C.

EXAMPLE 8

A solution of 2.4 grams of sodium hydroxide in 20 cubic centimetres of water to a solution of 7.9 grams of O-propionoylthiamine chloride hydrochloride in 20 cubic centimetres, of water. After the resulting solution had stood for 30 minutes, sodium hexamethylene-1,6-bisthiosulphate prepared in the same way as in Example 4 in 20 cubic centimetres of water was added to the above-obtained solution while stirring to give a yellow oily substance. The oily substance was treated in the same way as in the preceding Examples to yield 4.5 grams of hexamethylene-1,6-bis-(propionoylthiamine disulphide) melting at 100—102°C.

EXAMPLE 9

Sodium hexamethylene-1,6-bisthiosulphate was prepared by the reaction of 2.4 grams of hexamethylene-1,6-dibromide with 5 grams of sodium thiosulphate in the same way as in Example 4.

A solution of 2.4 grams of sodium hydroxide in 20 cubic centimetres of water was added to a solution of 10.6 grams of O-benzoylthiamine bromide hydrobromide in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes a solution of the above-obtained sodium hexamethylene-1,6-bisthiosulphate in 20 cubic centimetres of water was added thereto to give a yellow oily substance. Thereafter the oily substance was treated in the same way as in the preceding Examples to obtain 3.5 grams of hexamethylene-1,6-bis(benzoylthiamine disulphide) as a colourless powder melting at 132—133° C.

EXAMPLE 10

Sodium octamethylene-1,8-bisthiosulphate was prepared by the reaction of 1.3 gram of octamethylene-1,8-dibromide with 2.5 grams of sodium thiosulphate in the same way as in Example 3.

A solution of 1.3 gram of sodium hydroxide in 10 cubic centimetres of water was added to a solution of 5.0 grams of O-ethoxycarbonylthiamine bromide hydrobrimide in 10 cubic centimetres of water. After the resultant solution had stood for 30 minutes, a solution of the above-obtained sodium octamethylene-1,8-bisthiosulphate in 20 cubic centimetres of water was added thereto to give a yellow oily substance. Thereafter the oily substance was treated in the same was as in the preceding Examples to obtain 2.7 grams of octamethylene-1,8-bis (ethoxycarbonylthiamine disulphide) melting at 65—67°C.

EXAMPLE 11

Sodium octamethylene-1,8-bisthiosulphate was prepared by the reaction of 2.7 grams of octamethylene-1,8-dibromide with 5.0 grams of sodium thiosulphate in the same way as in Example 3.

A solution of 2.5 grams of sodium hydroxide in 20 cubic centimetres of water was

added to a solution of 7.6 grams of O-acetylthiamine chloride hydrochloride in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes, a solution of the above-obtained sodium octamethylene-1,8-bisthiosulphate in 40 cubic centimetres of water was added thereto to give a yellow oily substance. Thereafter the oily substance was treated in the same way as in the preceding Examples to obtain 6.5 grams of octamethylene-1,8-bis-(acetylthiamine disulphide) melting at 101—103°C.

EXAMPLE 12

Sodium octamethylene-1,8-bisthiosulphate was prepared by the reaction of 2.7 grams of octamethylene-1,8-dibromide with 5 grams of sodium thiosulphate in the same way as in Example 3.

A solution of 2.5 grams of soidum hydroxide in 20 cubic centimetres of water was addded to a solution of 8 grams of O-propionoylthiamine chloride hydrochloride in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes, a solution of the above-obtained sodium octamethylene-1,8-bisthiosulphate in 40 cubic centimetres of water was added thereto to give a yellow oily substance. Thereafter the oily substance was treated in the same way as in the preceding Examples to obtained 7.2 grams of octamethylene-1,8-bis-(propionoylthiamine disulphide) melting at 103—106°C.

EXAMPLE 13

Sodium octamethylene-1,8-bisthiosulphate was prepared by the reaction of 1.3 gram of octamethylene-1,8-dibromide with 2.5 grams of sodium thiosulphate in the same way as in Example 3.

A solution of 1.3 gram of sodium hydroxide in 20 cubic centimetres of water was added to a solution of 5.3 grams of O-benzoylthiamine bromide hydrobromide in 15 cubic centimetres of water. After the resultant solution had stood for 30 minutes, a solution of the above-obtained sodium octamethylene-1,8-bisthiosulphate in 20 cubic centimetres of water was added thereto to give yellow oily substance. Thereafter the oily substance was treated in the same way as in the preceding Examples to yield 3.2 grams of octamethylene-1,8-bis-(benzoylthiamine disulphide) melting at 105—107°C.

EXAMPLE 14

Sodium decamethylene-1,10-bisthiosulphate was prepared by the reaction of 3 grams of decamethylene-1,10-dibromide with 5 grams of sodium thiosulphate in the same way as in Example 1.

A solution of 2.5 grams of sodium hydroxide in 20 cubic centimetres of water was added to a solution of 7.6 grams of O-acetylthiamine chloride hydrochloride in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes, a solution of the above-obtained sodium decamethylene-1,10-bisthiosulphate in 50 cubic centimetres of water was added thereto to give a yellow oily substance. Thereafter the oily substance was treated in the same way as in the preceding Examples to obtain 5.8 grams of decamethylene-1,10-bis(acetylthiamine disulphide) as colourless crystals melting at 97—99°C.

EXAMPLE 15

Sodium-oct-2-enylene-1,8-bisthiosulphate was prepared by the reaction of 4 grams of oct-2-enylene-1,8-dibromide with 7.3 grams of sodium thiosulphate in the same way as in Example 1.

A solution of 3.6 grams of sodium hydroxide in 26 cubic centimetres of water was added to a solution of 10 grams of thiamine chloride hydrochloride in 20 cubic centimetres of water. After the resultant solution had stood for 30 minutes, a solution of the above-obtained sodium oct-2-enylene-1,8-bisthiosulphate in 30 cubic centimetres of water was added thereto to give an oily substance. Thereafter the oily substance was treated in the same way as in the preceding Examples to obtain 5.5 grams of oct-2-enylene-1,8-bis-(thiamine disulphide) melting at 127—132°C.

EXAMPLE 16

11 grams of phosphorus pentoxide were added dropwise to a solution of 5 grams of octamethylene-1,8-bisthiamine disulphide in 50 cubic centimetres of formic acid while the solution was stirred and cooled with ice. After the reaction mixture had stood overnight, formic acid was distilled off under reduced pressure. The residual oil was poured into ice-water, and then aqueous mixture was made alkaline with potassium carbonate give an oily substance.

The resulting oil was extracted with ethyl acetate, and the ethyl acetate layer was washed with water and dried. Then, the solvent was evaporated. Ether was added to

the residual oil, obtained and the solution was allowed to stand overnight while cooling to give 3 grams of octamethylene-1,8-bis-(formylthiamine disulphide) as colourless crystals. Recrystalisation from a mixture of ethyl acetate and ether yielded crystals melting at 92—95°C.

EXAMPLE 17

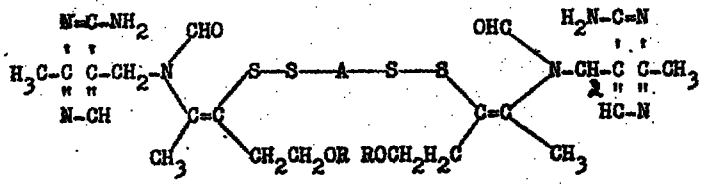
10.2 grams of acetic anhydride was added dropwise to a solution of 36.9 grams of octamethylene-1,8-bis-(thiamine disulphide) in 500 grams of pyridine while cooling. After the resulting reaction mixture had stood overnight, pyridine was evaporated under reduced pressure. The obtained residual oily substance was extracted with ethyl acetate. After the ethyl acetate layer had been washed with 10% aqueous sodium hydrogen carbonate solution and then water and dried, the solvent was evaporated and then ether was added to the residue to give 35 grams of octamethylene-1,8-bis-(acetylthiamine disulphide) melting at 101—103°C.

EXAMPLE 18

9 grams of benzoyl chloride were added dropwise while cooling to a solution of 11.1 grams of octamethylene-1,8-(thiamine disulphide) in 200 grams of pyridine. After the resulting reaction mixture had stood overnight, pyridine was evaporated under reduced pressure. Thereafter the oily substance obtained was treated in the same way as in Example 17 to give 10 grams of octamethylene-1,8-bis(benzoylthiamine disulphide) melting at 105—107°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:



wherein R is a hydrogen atom, a carboxylic acid acyl group containing up to seven carbon atoms, an alkoxycarbonyl group having up to seven carbon atoms or a phosphono group, and A is a saturated or unsaturated alkylene group containing from 4 to 20 carbon atoms.

2. Compounds as claimed in claim 1, wherein the alkylene group A contains from 6 to 10 carbon atoms.

3. Compounds as claimed in claim 1, wherein A is pentamethylene group.

4. Compounds as claimed in claim 1, wherein A is hexamethylene group.

5. Compounds as claimed in claim 1, wherein A is octamethylene group.

6. Compounds as claimed in claim 1, wherein A is decamethylene group.

7. Compounds as claimed in claim 1, wherein A is hept-2-enylene group.

8. Compounds as claimed in claim 1, wherein A is oct-2-enylene group.

9. Compounds as claimed in claim 1, wherein R is a formyl, acetyl, propionoyl, benzoyl or ethoxycarbonyl group.

10. Pentamethylene-1,5-bis-(thiamine disulphide)

11. Hexamethylene-1,6-bis-(thiamine disulphide)

12. Hexamethylene-1,6-bis-(acetylthiamine disulphide)

13. Hexamethylene-1,6-bis-(ethoxycarbonylthiamine disulphide)

14. Hexamethylene-1,6-bis-(propionoylthiamine disulphide)

15. Hexamethylene-1,6-bis-(benzoylthiamine disulphide)

16. Hept-2-enylene-1,7-bis-(thiamine disulphide)

17. Octamethylene-1,8-bis-(thiamine disulphide)

18. Octamethylene-1,8-bis-(formylthiamine disulphide)

19. Octamethylene-1,8-bis-(acetylthiamine disulphide)

20. Oct-2-enylene bis-(thiamine disulphide)

21. Octamethylene-1,8-bis-(ethoxycarbonylthiamine disulphide)

22. Octamethylene-1,8-bis-(propionoylthiamine disulphide)

23. Octamethylene-1,8-bis-(benzoylthiamine disulphide)

24. Decamethylene-1,10-bis-(thiamine disulphide)

25. Decamethylene-1,10-bis-(acetylthiamine disulphide)

26. A process for the preparation of a compound of the general formula given

the residual oil, obtained and the solution was allowed to stand overnight while cooling to give 3 grams of octamethylene-1,8-bis-(formylthiamine disulphide) as colourless crystals. Recrystalisation from a mixture of ethyl acetate and ether yielded crystals melting at 92—95°C.

EXAMPLE 17

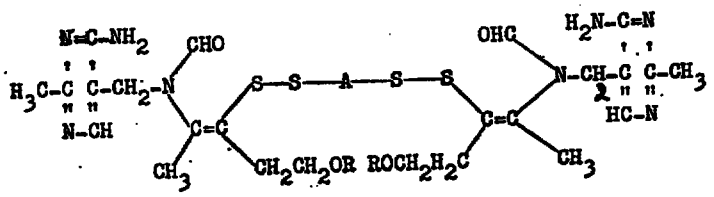
10.2 grams of acetic anhydride was added dropwise to a solution of 36.9 grams of octamethylene-1,8-bis-(thiamine disulphide) in 500 grams of pyridine while cooling. After the resulting reaction mixture had stood overnight, pyridine was evaporated under reduced pressure. The obtained residual oily substance was extracted with ethyl acetate. After the ethyl acetate layer had been washed with 10% aqueous sodium hydrogen carbonate solution and then water and dried, the solvent was evaporated and then ether was added to the residue to give 35 grams of octamethylene-1,8-bis-(acetylthiamine disulphide) melting at 101—103°C.

EXAMPLE 18

9 grams of benzoyl chloride were added dropwise while cooling to a solution of 11.1 grams of octamethylene-1,8-(thiamine disulphide) in 200 grams of pyridine. After the resulting reaction mixture had stood overnight, pyridine was evaporated under reduced pressure. Thereafter the oily substance obtained was treated in the same way as in Example 17 to give 10 grams of octamethylene-1,8-bis(benzoylthiamine disulphide) melting at 105—107°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:



wherein R is a hydrogen atom, a carboxylic acid acyl group containing up to seven carbon atoms, an alkoxycarbonyl group having up to seven carbon atoms or a phosphono group, and A is a saturated or unsaturated alkylene group containing from 4 to 20 carbon atoms.

2. Compounds as claimed in claim 1, wherein the alkylene group A contains from 6 to 10 carbon atoms.

3. Compounds as claimed in claim 1, wherein A is pentamethylene group.

4. Compounds as claimed in claim 1, wherein A is hexamethylene group.

5. Compounds as claimed in claim 1, wherein A is octamethylene group.

6. Compounds as claimed in claim 1, wherein A is decamethylene group.

7. Compounds as claimed in claim 1, wherein A is hept-2-enylene group.

8. Compounds as claimed in claim 1, wherein A is oct-2-enylene group.

9. Compounds as claimed in claim 1, wherein R is a formyl, acetyl, propionoyl, benzoyl or ethoxycarbonyl group.

10. Pentamethylene-1,5-bis-(thiamine disulphide)

11. Hexamethylene-1,6-bis-(thiamine disulphide)

12. Hexamethylene-1,6-bis-(acetylthiamine disulphide)

13. Hexamethylene-1,6-bis-(ethoxycarbonylthiamine disulphide)

14. Hexamethylene-1,6-bis-(propionoylthiamine disulphide)

15. Hexamethylene-1,6-bis-(benzoylthiamine disulphide)

16. Hept-2-enylene-1,7-bis-(thiamine disulphide)

17. Octamethylene-1,8-bis-(thiamine disulphide)

18. Octamethylene-1,8-bis-(formylthiamine disulphide)

19. Octamethylene-1,8-bis-(acetylthiamine disulphide)

20. Oct-2-enylene bis-(thiamine disulphide)

21. Octamethylene-1,8-bis-(ethoxycarbonylthiamine disulphide)

22. Octamethylene-1,8-bis-(propionoylthiamine disulphide)

23. Octamethylene-1,8-bis-(benzoylthiamine disulphide)

24. Decamethylene-1,10-bis-(thiamine disulphide)

25. Decamethylene-1,10-bis-(acetylthiamine disulphide)

26. A process for the preparation of a compound of the general formula given

* C L M S *

in claim 1, which comprises reacting thiamine or an O-ester thereof at a non-acidic pH with a compound of the general formula

$$X—S—A—S—X$$

in which X is $—SO_3M$, $—SO_2R^1$, $—SOR^1$, —SCN or a halogen atom, M is an alkali metal or one valency of an alkaline earth metal and R^1 is a hydrocarbon residue having up to seven carbon atoms.

27. A process as claimed in claim 26, wherein the pH is maintained greater than 7 by adding an inorganic base.

28. A process as claimed in claim 26, substantially as described with reference to any of the Examples.

29. Compounds of the general formula given in claim 1, when prepared by the process claimed in any of claims 26 to 28.

30. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 25 and a pharmaceutical diluent or carrier.

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