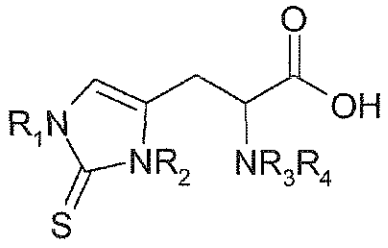
Organomet. Chem. 529, 295-299 (1997)) which is also very dangerous on an industrial scale.

Thus, there is a real need to develop a novel method for the synthesis of 2-thiohistidine and derivatives thereof that is applicable at the industrial level, *i.e.*, that does not have purification difficulties, that does not use products or solvents that are dangerous or toxic for humans and the environment, and that enables access to the product, on an industrial scale, with a good yield and at a low cost.

In one aspect of t~~T~~he present invention ~~thus has as an object~~, there is provided a method for the synthesis of a 2-thiohistidine derivative of the following formula (I):



(I),

or a physiologically acceptable salt, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportions thereof, in particular a mixture of enantiomers, and notably a racemic mixture thereof, wherein:

- R_1 and R_2 represent, independently of each other, a hydrogen atom or a (C_1-C_4)alkyl group such as methyl, at least one of the groups R_1 and R_2 representing a hydrogen atom, and advantageously each representing a hydrogen atom, and
- R_3 and R_4 represent, independently of each other, a hydrogen atom or a (C_1-C_4)alkyl group such as methyl,

comprising the following successive steps:

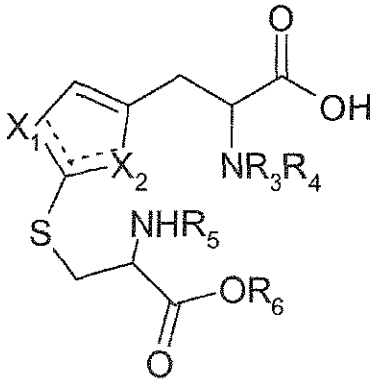
(i) cleavage reaction of a compound of following formula (II):

and in particular with cysteine, dithiothreitol, 2-mercaptoethanol, 2-mercaptopropionic acid, 3-mercaptopropionic acid or thioglycolic acid, and preferably with 3-mercaptopropionic acid, at a temperature higher than or equal to 60°C,
to yield a compound of the formula (Ia), and
(c2) separation of the compound of the formula (Ia) obtained in the preceding step (b2) from the reaction medium.

The steps (a2), (b2) and (c2) correspond to the preceding steps (a1), (b1) and (c1), respectively.

The compounds of the formula (IIa) represent particular forms of the compound of the formula (II). Similarly, the compounds of the formula (IIIa) represent particular forms of the compound of the formula (III).

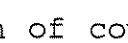
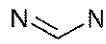
The present disclosure~~invention~~ also relates to~~has as an object~~ a compound of the following formula (II):



(II),

or a physiologically acceptable salt, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportions thereof, in particular a mixture of enantiomers, and notably a racemic mixture thereof, wherein:

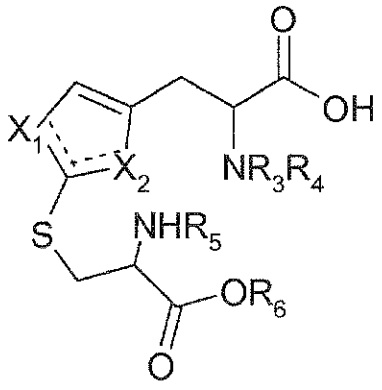
- $X_1 \overset{\cdots}{=} X_2$ represents $R_1N{=}N$ or $N{=}NR_2$, and
- R_1, R_2, R_3, R_4, R_5 and R_6 are such as defined above,

to the exclusion of compound wherein  represents  or , and R_3 and R_4 each represent a hydrogen atom.

The excluded compound is described in: Ito et al., *J. Org. Chem.* 1985, 50, 3636-3638.

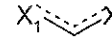
This compound can be in particular 2-{2-[(2-ammonio-2-carboxyethyl)thio]-1*H*-imidazol-4-yl}-1-carboxy-*N*,*N*-dimethylethanaminium ($HisNMe_2$-Cys) or the dihydrochloride thereof, and 2-{2-[(2-ammonio-2-carboxyethyl)thio]-1*H*-imidazol-4-yl}-1-carboxy-*N*-methylethanaminium (HisNHMe-Cys) or the dihydrochloride thereof.

The present disclosure~~invention~~ also relates to~~has as an object~~ a method for the preparation of a compound of the following formula (II):



(II),

or a physiologically acceptable salt, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportions thereof, in particular a mixture of enantiomers, and notably a racemic mixture thereof, wherein:

-  represents  or , and
- R_1, R_2, R_3, R_4, R_5 and R_6 are such as defined above,

by reaction of an acid addition salt, to the exclusion of a hydriodic acid salt, of a compound of the formula (III) such as defined above, or a tautomer, a