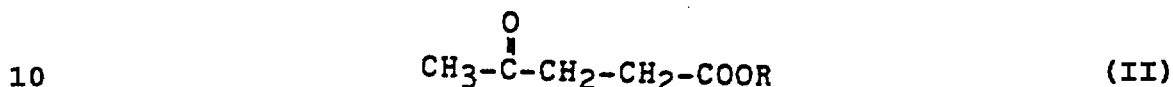


Process for the preparation of 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetic acid and esters thereof

The present invention relates to a process for the preparation of 2-mercapto-4-methyl-1,3-thiazole-5-acetic acid and alkyl esters thereof, of the formula I



in which R denotes hydrogen or a C₁-C₄-alkyl radical, which comprises reacting a levulinic acid ester of the formula II



in which R denotes a C₁-C₄-alkyl radical, with 0.7-1.5 mol of a halogenating agent per mole of levulinic acid ester at a temperature of from -20°C to +150°C, separating off from the resulting isomer mixture the 3-halogeno isomer of the formula III



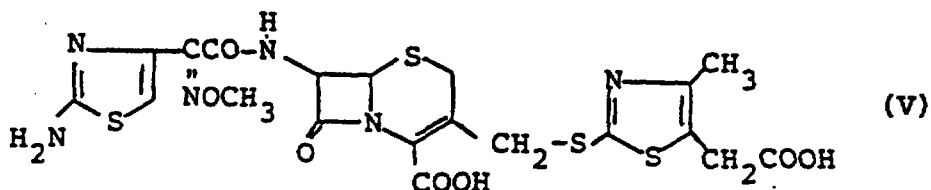
in which R has the meaning given and Hal denotes a chlorine, bromine or iodine atom, reacting this isomer with ammonium dithiocarbamate of the formula IV



to give the compound of the formula I in which R represents a C₁-C₄-alkyl radical, and if appropriate converting the ester of the formula I into the free acid.

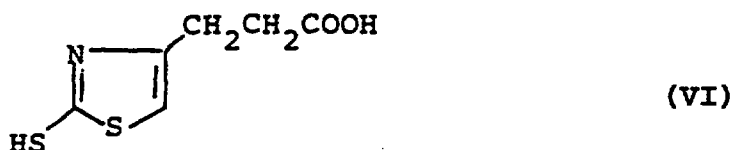
The compound of the formula I is already known. It can be

used, for example, as a molecular unit for the preparation of the antibiotic cefodizime (German Offenlegungsschrift 3,117,438) of the formula V



5 and also for the preparation of imunomodulators (German Offenlegungsschrift 3,508,665 and German Offenlegungsschrift 3,508,666).

10 In order to obtain a cefodizime (V) which meets specifications, a mercaptomethylthiazole acid of sufficiently high purity must be employed in the synthesis. In particular, the isomeric compound 2-mercaptothiazole-4-propionic acid (VI)



and coloring impurities have a troublesome effect.

15 Processes for the preparation of compounds of the formula I are known in the literature.
Thus, for example, Y. Hara and S. Fujise (Pharm. Bull. (Japan), Volume 2 (1954), pages 156-158) describe the reaction of ethyl 3-bromolevulinate with ammonium dithiocarbamate to give a compound of the present formula I in
20 which R denotes the ethyl radical. However, this process leads to very unsatisfactory yields. Relatively large amounts of ether are employed at the ester and acid preparation stage, and this is highly undesirable from
25 the safety point of view because of the possible formation of peroxide and its high flammability. Several recrystallizations from ethanol are carried out for purification of the product, and in the case of the acid, as has been demonstrated, this leads to renewed ester

formation by autocatalysis.

The process according to P. Lechat et al. (Therapie 26(3), 497-509 (1971)) has the same disadvantages as the process described above.

- 5 A process is furthermore known from German Offenlegungsschrift 3,117,438 for the preparation of compounds of the abovementioned formula I, which comprises first esterifying 3-halogenolevulinic acid and then reacting the resulting ester with ammonium dithiocarbamate.
- 10 In the prior halogenation of levulinic acid, in particular chlorination, for example with chlorine or sulfuryl chloride, however, a mixture of 3-chlorolevulinic acid, 3,3-dichlorolevulinic acid, 5-chlorolevulinic acid, 3,5-dichlorolevulinic acid, 5,5-dichlorolevulinic acid, other
15 unknown by-products and unreacted levulinic acid is obtained. If this mixture is reacted with ammonium dithiocarbamate of the abovementioned formula IV for preparation of the mercaptomethylthiazole acid of the abovementioned formula I, a colored crude product contaminated with by-products, in particular 2-mercapto-1,3-
20 thiazole-4-propionic acid of the formula VI, is obtained. The coloring compounds and the isomer of the formula VI can be separated off by several purification steps (reprecipitation and recrystallization from organic
25 solvents), and a 2-mercapto-4-methyl-thiazole-acetic acid which can be used is thus obtained. However, very unsatisfactory yields of only about 15 - 20% of theory, based on the levulinic acid employed, are achieved in this process.
- 30 The use of organic solvents moreover leads to high working up costs and environmental pollution.

Since the dichloro compounds likewise react with ammonium dithiocarbamate, in this case about 2.5 mol of ammonium dithiocarbamate must be employed per mol of 3-chloro-
35 levulinic acid employed.

Surprisingly, it has now been found that 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetic acid or C₁-C₄-alkyl esters thereof can be prepared in an isomer-free form with high yields by a process in which, instead of levulinic acid,
5 the alkyl levulinate of the formula II



in which R denotes C₁-C₄-alkyl, is halogenated and, after the resulting 3-halogeno-levulinic acid ester has been separated off by rectification, this is reacted with
10 ammonium dithiocarbamate.

The introduction of the halogen atom, which can be chlorine, bromine or iodine, into the 3-position is carried out by customary methods. Preferably, the levulinic acid ester is chlorinated, and in particular
15 especially by reaction with elemental chlorine or with sulfur chloride.

The reaction can be carried out without or in the presence of an inorganic or organic solvent.

The amount of halogenating agent here is about 0.7 -
20 1.5 mol per mol of levulinic acid ester, but preferably about 1.0 - 1.3 mol. The reaction temperature can vary within fairly wide ranges. In general, it is between -20°C and about +150°C, but preferably between -5°C and about +80°C.

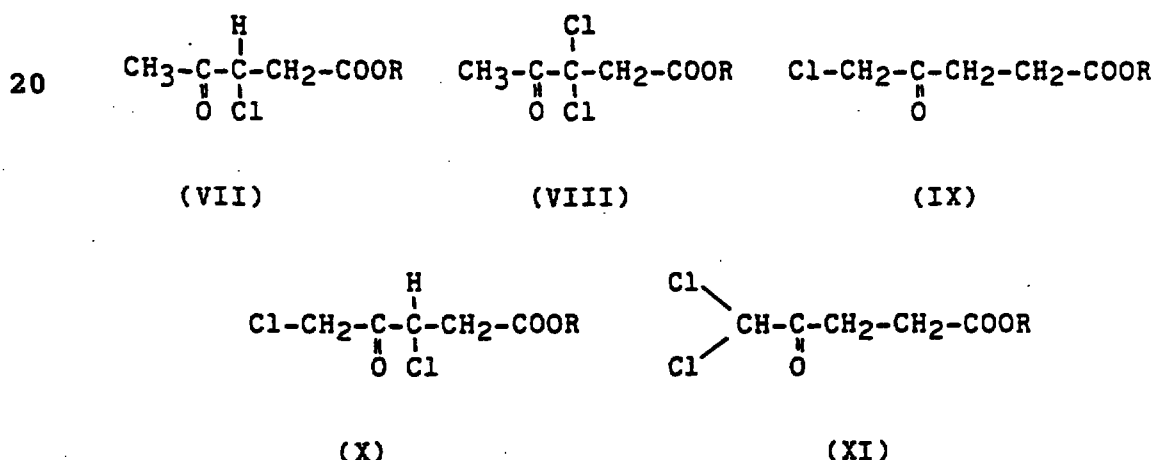
25 Water or hydrochloric acid may be mentioned as examples of preferred inorganic diluents. Preferred organic diluents which may be mentioned here as examples are:
C₅-C₇-aliphatic and C₆-C₈-cycloaliphatic hydrocarbons, such as, for example, pentane, 2-methylbutane, hexane,
30 2,2-dimethylbutane, 2,3-dimethylbutane, 2-methylpentane, 3-methylpentane, heptane, cyclohexane, methylcyclohexane, 1,2-dimethylcyclohexane, 1,3-dimethylcyclohexane and 1,4-dimethylcyclohexane; aromatic hydrocarbons, such as, for

example, toluene, xylenes and isopropylbenzene; aliphatic and aromatic halogenohydrocarbons, such as, for example, tetrachloroethylene, 1,1,2,2- and 1,1,1,2-tetrachloroethane, methylene chloride, dichloropropane, carbon
 5 tetrachloride, 1,1,2-trichloro-1,2,2-trifluoroethane, 1,2-dichloroethane, 1,1-dichloroethane and chlorobenzene.

Particularly preferred diluents are aliphatic and cycloaliphatic hydrocarbons.

The amount of diluent employed, if the reaction is not
 10 carried out without a diluent, can vary within wide ranges.

The desired 3-chlorolevulinic acid ester (VII) is preferably formed in the chlorinating method described. 3,3-Dichlorolevulinic acid ester (VIII), 5-chlorolevulinic
 15 acid ester (IX), 3,5-dichlorolevulinic acid ester (X) and 5,5-dichlorolevulinic acid ester (XI) are formed as a by-product in noticeable amounts - depending on the variation of the conditions. Unreacted levulinic acid ester can moreover also be present in the chlorination mixture.



The hydrogen chloride formed is separated off from the reaction mixture by washing with water and subsequent phase separation, blowing out with carrier gas or distillation.

The diluent used can likewise be separated off by phase separation or distillation by processes customary in laboratories.

5 The actual reaction mixture prepurified in this way is subjected to rectification in vacuo. In contrast to the reaction mixture formed on halogenation, for example chlorination, of levulinic acid, in the process according to the invention it is possible to separate off all the interfering impurities which lead to by-products. The
10 mixture is separated as follows:

First runnings:	levulinic acid ester as the main constituent
Main runnings:	3-chlorolevulinic acid ester as the main constituent, contaminated with 3,3-dichlorolevulinic acid ester
15 Residue:	5-chlorolevulinic acid ester, 3,5-dichlorolevulinic acid ester, 20 5,5-dichlorolevulinic acid ester and other chlorinated by-products.

25 The first runnings can be employed in renewed chlorination to increase the yield.

In order to obtain high yields of 3-chlorolevulinic acid ester (VII), the majority of the 3,3-dichlorolevulinic ester (VIII) must also be distilled off during the distillation, since this compound does not have a great
30 difference in boiling point to (VII).

Surprisingly, in the subsequent reaction under the chosen conditions (VIII) does not react with the ammonium dithiocarbamate to give troublesome thiazole derivatives. According to the invention, the main runnings from the

rectification are reacted with ammonium dithiocarbamate in water, advantageously with the addition of a solvent which is only sparingly miscible or immiscible with water, if appropriate with the addition of a phase transfer catalyst. After acidification with a mineral acid, the ester is isolated by customary laboratory processes.

The reaction temperature is in general in the range from about -10 to +60°C, but preferably between +10 and +30°C.

Examples which may be mentioned of solvents which are only sparingly or immiscible with water are:

aliphatic and cycloaliphatic hydrocarbons, such as, for example, pentane, 2-methylbutane, 2,2-dimethylbutane, 2,3-dimethylbutane, 2-methylpentane, 3-methylpentane, heptane, cyclohexane, methylcyclohexane, 1,2-dimethylcyclohexane, 1,3-dimethylcyclohexane and 1,4-dimethylcyclohexane; aromatic hydrocarbons, such as, for example, toluene, xylene and isopropylbenzene; aliphatic and aromatic halogenohydrocarbons, such as, for example, tetrachloroethylene, 1,1,2,2- and 1,1,1,2-tetrachloroethane, methylene chloride, dichloropropane, carbon tetrachloride, 1,1,2-trichloro-1,2,2-trifluoroethane, trichlorofluoromethane, 1,2-dichloroethane, 1,1-dichloroethane and chlorobenzene; alcohols, such as, for example, butanol, pentanol, isobutanol and the like; esters, such as, for example, butyl acetate, amyl acetate and the like; and ethers, such as, for example, diisopropyl ether, diisoamyl ether, methyl t-butyl ether, di-n-butyl ether, ethylene glycol dimethyl ether, tetrahydrofuran, dioxane and anisole.

The nature and amount of the solvent which is insoluble or only sparingly soluble in water are chosen according to the solubility of the mercaptomethylthiazoleacetic acid ester to be prepared.

The use of phase transfer catalysts may be advantageous to accelerate the reaction. Examples which may be

mentioned are ammonium salts, such as tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, tetrabutylammonium hydrogen sulfate, benzyl-trimethyl-ammonium bromide, benzyl-dimethyl-n-dodecyl-ammonium bromide or trioctyl-methyl-ammonium chloride, or quaternary phosphonium compounds, such as, for example, ethyl-trioctyl-phosphonium bromide and hexadecyl-tri-butylphosphonium bromide.

Examples of mineral acids which may be mentioned are: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like. The mercaptomethylthiazole ester thus obtained is practically free from isomers and can be converted into the free mercaptomethylthiazole-acetic acid by hydrolysis in aqueous solution and subsequent acidification. The hydrolysis temperature can vary within wide ranges. It is in general about -10 to about +100°C, preferably 15 - 40°C.

Aqueous solutions of alkali metal hydroxides, such as, for example, sodium hydroxide and potassium hydroxide, preferably about 2 mol per mol of ester, are used for the hydrolysis.

Examples of mineral acids which may be mentioned are: hydrochloric acid, hydrobromic acid, sulfuric acid and nitric acid. The mercaptomethylthiazole acid thus prepared completely meets the requirements for further processing to cefodizime (V).

The following examples are intended to illustrate the invention, but without limiting it.

Example 1

Preparation of methyl 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetate

390 ml of n-heptane are added to 130 g of methyl

levulinate. 92 ml of sulfuryl chloride are added dropwise at about 70°C in the course of 15 minutes and the mixture is subsequently stirred for a further 3 hours. The n-heptane is then distilled off under normal pressure to give about 168 g of chlorination mixture as the residue. The chlorination mixture is then separated in vacuo under about 50 mbar over a Raschig column.

	First runnings:	13 g (content: 10 g of methyl levulinate)
10	Main runnings:	120 g
	Residue:	65 g

50 ml of n-butanol, 100 ml of water and 68 g of ammonium dithiocarbamate are added to the main runnings, while stirring thoroughly, 1 g of tetrabutylammonium chloride are added and the mixture is allowed to after-react at 25-30°C for 3 hours. A pH of about 0.5 - 1.0 is established by addition of about 10 ml of 37% strength hydrochloric acid, the mixture is cooled to 0 - 5°C and the ester formed is isolated. The ester is washed with cold n-butanol and water.

After drying, 111.6 g of methyl 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetate are obtained. This corresponds to a yield of 59.6% of theory, based on the methyl levulinate consumed.

25 Example 2

Preparation of ethyl 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetate

144 g of ethyl levulinate are cooled to 0 - 5°C. 74 g of chlorine are introduced at this temperature in the course of 3 hours. The chlorination mixture is then poured onto 200 ml of ice-water. 180 g of chlorination mixture are obtained by separating off the organic phase, and are subsequently purified by distillation in vacuo under

about 15 mbar over a column packed with Raschig rings.

First runnings: 22 g (content: 18 g of ethyl levulin-
ate)

Main runnings: 105 g

5 Residue: 53 g

45 ml of butanol, 90 ml of water and 55 g of ammonium dithiocarbamate are added to the main runnings, while stirring thoroughly, 1 g of tetrabutylammonium chloride is added and the mixture is allowed to after-react at
10 25 - 30°C for a further 3 hours. The pH is brought to about 0.5 to 1.0 by addition of about 8 ml of 37% strength hydrochloric acid, the mixture is cooled to 0 - 5°C and the ester formed is then filtered off with suction. After washing with cold n-butanol and water, the
15 product is dried. 98.6 g of ethyl 2-mercapto-4-methyl-thiazol-5-yl-acetate are obtained. This corresponds to a yield of 51.9% of theory, based on the ethyl levulinate consumed.

Example 3

20 Preparation of 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetic acid

108.5 g of ethyl 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetate are suspended in 200 ml of water, and 127 g of
33% strength sodium hydroxide solution are added at 20
25 -30°C. The mixture is then subsequently stirred at this temperature for a further 2 - 3 hours. The pH is then brought to 7 - 7.5 by addition of 54 g of 37% strength hydrochloric acid. After clarification with 5 g of active charcoal, the mixture is acidified to pH 0.5 - 1.0 by
30 further addition of 51 g of 37% strength hydrochloric acid. The 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetic acid which has precipitated is filtered off with suction, after cooling to 0 - 5°C, and then washed with cold water. After drying, 90.7 g of pure acid are obtained.
35 This corresponds to a yield of 96% of theory, based on

the ethyl 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetate
employed.



Patent Claims:

1. A process for the preparation of 2-mercapto-4-methyl-1,3-thiazol-5-yl-acetic acid or an alkyl ester thereof, of the formula I



in which R denotes hydrogen or C₁-C₄-alkyl, which comprises

- a) reacting a levulinic acid ester of the formula II



10 in which R denotes C₁-C₄-alkyl with 0.7 - 1.5 mol of a halogenating agent per mole of levulinic acid ester at a temperature of from -20°C to +150°C

- 15 b) separating off from the resulting reaction mixture, by rectification, a fraction which essentially comprises the desired 3-halo compound of the formula III



20 and in a small amount the 3,3-dihalo compound of the formula XIII



in which R has the abovementioned meaning and Hal denotes chlorine, bromine or iodine,

- 25 c) reacting the fraction obtained according to step b) with ammonium dithiocarbamate to give a compound of the formula I in which R denotes C₁-C₄-alkyl, and
d) if appropriate converting the resulting ester



into a compound of the formula I in which R denotes hydrogen, by customary methods.

2. The process as claimed in claim 1, wherein the compound of the formula II is reacted with a chlorinating agent.
3. The process as claimed in claim 2, wherein the reaction is carried out with elemental chlorine or with sulfuryl chloride with or without a diluent.
4. The process as claimed in claim 3, wherein the chlorination is carried out with sulfuryl chloride in the presence of an aliphatic or cycloaliphatic hydrocarbon.
5. The process as claimed in claim 1, wherein the rectification is carried out under reduced pressure.
6. The process as claimed in claim 1, wherein the reaction with ammonium dithiocarbamate is carried out with addition of a solvent which is immiscible or sparingly miscible with water.
7. The process as claimed in claim 6, wherein a C₄- or C₅-alkanol is used as the solvent.
8. The process as claimed in claim 6, wherein the reaction with ammonium dithiocarbamate is carried out in the presence of a phase transfer catalyst.
9. The process as claimed in claim 8, wherein a quaternary ammonium salt or a quaternary phosphonium compound is used as the phase transfer catalyst.
10. The process as claimed in claims 6 to 9, wherein the reaction is carried out at a temperature of 10 - 30°C.