

PATENT SPECIFICATION

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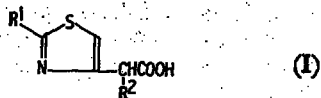
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(54) THIAZOLYLACETIC ACID DERIVATIVES

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 as TAKEDA CHEMICAL INDUSTRIES,
 LTD., of 27, Doshomachi, 2-chome, Higashi-
 ku, Osaka, Japan, a joint stock company
 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 thiazole deriva-
 tives, more particularly to thiazolylacetic acid
 derivatives, and to a process for their pre-
 paration.

Thus the present invention provides a
 thiazole compound of the general formula:



wherein R¹ represents an amino or hydroxyl
 group which may be protected, and
 R² represents an amino group which may be
 protected or a hydroxyl group, or



represents a group of the formula



where R⁵ represents a hydroxyl group which
 may be protected, provided that R² does not
 represent a hydroxyl group when R¹ repre-

sents an optionally protected hydroxyl group,
 or a salt or reactive derivative thereof.

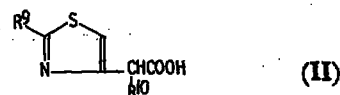
Specific Examples of such compounds are:

- (i) ethyl α - acetamido - α - [2 - (β , β , β -
 trichloroethoxy - carbonylamino)thiazol - 4 -
 yl]acetate; and
 (ii) α - chloro - acetamido - α - (2 - chloro-
 acetamidothiazol - 4 - yl)acetic acid.

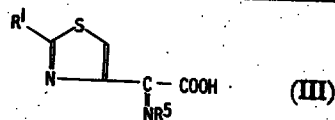
The reactive derivative referred to above
 is a derivative having enhanced reactivity in
 acylation reactions, as exemplified in our co-
 pending Application No. 24611/75, Serial
 No. 1536281, e.g. acid halides, acid
 anhydrides, mixed acid anhydrides, cyclic
 carboxy anhydrides, active amides and
 esters.

The symbol R⁵ means a hydroxyl group
 which may be protected. Any conventional
 protective groups for hydroxyl groups may be
 used so far as they do not disturb the reac-
 tions of this invention. There may generally
 be employed a lower alkyl group such as
 methyl or ethyl, an aryl group such as phenyl
 or thienyl, or an acyl group such as acetyl or
 benzoyl.

According to particular embodiments of the
 invention there are provided thiazole deriva-
 tives of formula:



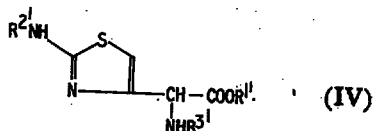
where each of R⁹ and R¹⁰ represents an
 amino or hydroxyl group, providing R⁹ and
 R¹⁰ do not both represent a hydroxyl group,
 or a salt or a reactive derivative thereof, and
 of the formula:



where R¹ represents an amino or hydroxyl group which may be protected and R⁵ represents a hydroxyl group which may be protected, or a salt or a reactive derivative thereof.

An example of a compound III is α -methoxyimino - α - [2 - (β , β , β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetic acid.

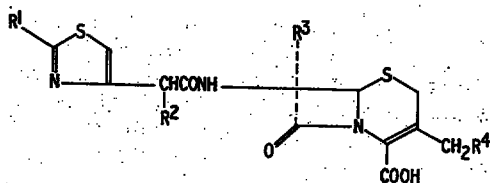
In a further embodiment the invention provides a 2 - aminothiazol - 4 - ylglycine derivative of general formula (IV)



where R^{2'}NH and NHR^{3'} are optionally protected amino groups and COOR^{1'} is an optionally protected carboxyl group.

These novel thiazole derivatives are useful intermediates for the preparation of certain cephem compounds which have antibiotic properties.

These cephem derivatives correspond to the general formula:

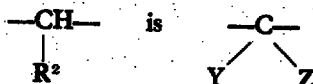


wherein R¹ and R² are as defined above, R³ represents hydrogen or a methoxy group, and R⁴ represents hydrogen or a residue of a nucleophilic compound, or a pharmaceutically acceptable salt or ester thereof.

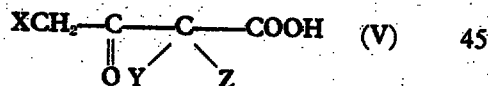
These cephem derivatives are novel compounds and they are described and claimed in our copending Application No. 24611/75, Serial No. 1536281. Our copending application also describes and claims the preparation of these cephem derivatives from the thiazole derivatives (I) according to the present invention.

The thiazole compounds of formula (I) may be prepared by

(1) in the case where R¹ is an amino or hydroxyl group which may be protected, and



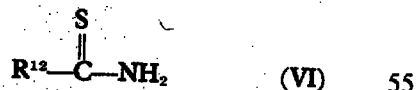
where Y and Z are defined below, reacting a compound of the formula:



wherein X represents a halogen atom, Y represents hydrogen and Z represents an amino group which may be protected, or Y and Z together represent a group of the formula:

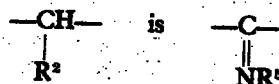


wherein R⁵ represents a hydroxyl group which may be protected, or a salt or ester thereof, with a compound of the formula:

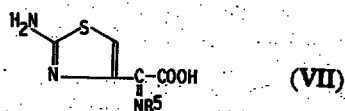


wherein R¹² represents a C₁-C₄ alkoxy group or an amino group which may be protected, followed by, if necessary, removal of the protective group,

(2) where R¹ is hydroxyl and



reacting a compound of the formula:



wherein R⁵ is as defined above, or a salt or ester thereof, with a diazotizing reagent, followed by, if necessary, removal of the protective group,

(3) where R₁ is amino or protected amino and R₂ is hydroxyl, reacting a compound of the formula:



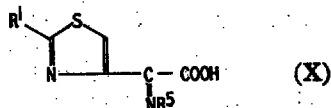
wherein R¹⁴ represents an amino group which may be protected, with a trihalogenoacetone in the presence of a base to obtain a compound of the formula:



wherein R¹⁴ is as defined above, subjecting

this compound to an addition reaction with hydrogen cyanide, acylating the cyanhydrin obtained and hydrolysing the resulting product, followed by, if necessary, removal of the protective group, or

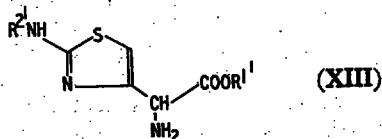
(4) where R^1 is an amino or hydroxyl group which may be protected and R^2 is amino, reducing a compound of the formula:



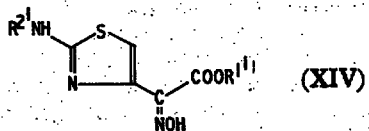
wherein R^1 and R^2 are as defined above, or a salt or ester thereof, followed by, if necessary, removal of the protective group.

Certain of the compounds of the formula V are described and claimed in our copending Application No. 28892/78, Serial No. 1536283 which is divided from the present Application.

In a particular embodiment the invention provides a process for producing a 2-aminothiazol-4-yl-glycine derivative of the general formula:

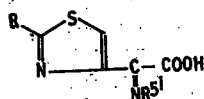


(wherein $-\text{COOR}^1$ and $\text{R}^2\text{NH}-$ are as defined below) which comprises reducing a 2-aminothiazole derivative of the general formula:

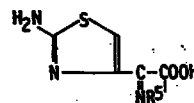


(wherein $-\text{COOR}^1$ is a carboxyl group which may optionally be protected, and $\text{R}^2\text{NH}-$ is an amino group which may optionally be protected) and, if necessary, removing the protective group or groups.

In another embodiment, the invention provides a process for preparing a compound of the formula

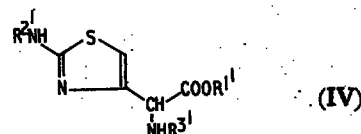


wherein R represents a protected amino group and R^2 represents a hydroxyl, methoxy or ethoxy group, or a salt, an ester or a reactive derivative thereof, which comprises introducing a protective group onto a compound of the formula



wherein the symbol R^2 has the same meaning as mentioned above, or a salt, an ester or a reactive derivative thereof.

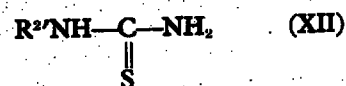
In another embodiment, the invention provides a process for producing a 2-aminothiazol-4-ylglycine derivative of the general formula:



(wherein $-\text{COOR}^1$, $\text{R}^2\text{NH}-$ and $\text{R}^3\text{NH}-$ are as defined below) which comprises reacting an α -amino- β -keto- γ -halogeno-butyric acid ester of the general formula:



(wherein X is a halogen atom; $-\text{COOR}^1$ is a carboxyl group which may optionally be protected; and $\text{R}^3\text{NH}-$ is an amino group which may optionally be protected) with a thiourea compound of the general formula:



(wherein $\text{R}^2\text{NH}-$ is an amino group which may optionally be protected) and, if necessary, removing the protective group or groups.

We have found that penicillin or cephalosporin compounds having an acyl group at the 6- or 7-position, as the case may be, derived from a product according to the present invention, display excellent antibiotic activity. The findings provided the impetus for the development of this invention.

In the above general formulae, $-\text{COOR}^1$ denotes a carboxyl group which may optionally be protected and, therefore, R^1 stands for a hydrogen atom or a protective group for the carboxyl function. The protective group may be any group that can be removed under mild conditions, e.g. under acid, alkaline or reducing conditions, and without interference with the thiazole nucleus. Thus, for example, such protective groups are selected from among those groups which are commonly employed as protective groups for carboxyl groups in the synthesis of peptides. Among such protective groups are alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl and tert-butyl; substituted alkyl groups such as β -methylsulfonyl, trichloroethyl and diphenyl-

methyle; aryl groups such as phenyl and tolyl; substituted aryl groups such as *p*-tert-butylphenyl and *p*-nitrophenyl; aralkyl groups such as benzyl, phenethyl and tolu benzyl (i.e. *o*-, *m*- or *p*-methylbenzyl); and substituted aralkyl groups such as *p*-methoxybenzyl and *p*-nitrobenzyl. R^2NH- and R^3NH- , respectively, represent an amino group which may optionally be protected and, therefore, R^2 and R^3 each represent a hydrogen atom or a protective group for the amino function. As such protective groups are employed those easily-removable protective groups for amino groups which are commonly employed in peptide chemistry. Thus, for example, there may be mentioned alkanoyl groups such as formyl, acetyl and propionyl; alkoxycarbonyl groups such as *t*-butoxycarbonyl; alkoxyalkylcarbonyl groups such as methoxyacetyl and methoxypropionyl; substituted alkoxycarbonyl groups such as trichloroethoxycarbonyl; alkoxycarbonylacetyl groups such as methoxycarbonylacetyl; aralkyloxycarbonyl groups such as benzyloxycarbonyl; and substituted aralkyloxycarbonyl groups such as *p*-nitrobenzyloxycarbonyl; to mention only those commonly employable. The symbol X stands for a halogen atom which may be chlorine, bromine, iodine or fluorine.

In one embodiment of the process of this invention, a 2-aminothiazole derivative XIV is reduced in the first place. As the procedure for reduction, there is employed one of the known reductive procedures, by which XIV may be converted to the contemplated compound XIII. Thus, for example, reduction with a catalyst (e.g. Raney nickel, platinum oxide, palladium-on-carbon, ruthenium-on-carbon, rhodium-on-carbon or copper chromium oxide, reducing means involving the use of nascent hydrogen as evolved by the combined use of a metal, e.g. sodium, amalgamated sodium or amalgamated aluminium, with water or an alcohol; reductive procedures involving the use of metal hydride complex compounds such as lithium aluminium hydride, diethylaluminium hydride, sodium aluminium hydride and sodium borohydride; reducing means which comprise treating the material compound with a metal, e.g. zinc or iron, in anhydrous acetic acid, formic acid or a water-miscible solvent and electrolytic reduction may be employed with advantage. The temperature and pressure of the reduction reaction, the type of solvent to be employed, the reaction time and other conditions are selected according to the particular species of starting (substrate) material and the reductive procedure selected. Following the reduction, the protective group or groups may be removed, if necessary, with or without prior isolation of the desired product.

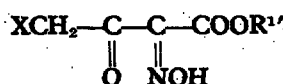
Removal of the protective groups may be

accomplished by one or another of the procedures which are routinely employed for removing various kinds of protective groups. For example, alkyl groups such as ethyl or propyl, may be easily removed by means of acid or alkali; diarylalkyl groups such as diphenylmethyl and alkoxyaralkyl groups such as *p*-methoxybenzyl may be easily removed by the action of acid; methylsulfonylalkyl groups such as β -methylsulfonylethyl by means of alkali; halogenoalkyl groups such as β,β,β -trichloroethyl by means of zinc and acid; and *p*-nitrophenylalkyl groups such as *p*-nitrobenzyl by means of catalytic reduction. Removal of protective groups R^2 , R^3 on amino groups may also easily be accomplished. For example, halogenoalkoxycarbonyl groups such as β,β,β -trichloroethoxycarbonyl may be easily removed by means of zinc and acid; formyl or tertiary alkoxy carbonyl groups such as *t*-butoxycarbonyl may be removed with acid; substituted aralkyloxycarbonyl groups such as *p*-nitrobenzyloxycarbonyl may be easily removed by catalytic reduction. Where the carboxyl and amino groups are both protected, removal of these protective groups may be simultaneously accomplished, or one of them may be removed before another in consideration of the types of protective groups. The resulting desired compound may be isolated and purified by procedures known *per se*, such as solvent extraction, phase transfer, pH adjustment, crystallization, recrystallization, distillation, chromatography and ion exchange. Being a mixture of D- and L-forms, the product XIII thus isolated may be resolved into the D- and L-compounds by converting it to a suitable optically active crystalline salt such as the tartrate, mandelate, malate or camphorsulfonate.

The desired compound (IV) of this invention may be produced by reacting an α -amino- β -keto- γ -halogenobutyric acid ester (XI) with a thiourea compound (XII) and, if necessary, removing the protective group or groups. In conducting the reaction, it is preferable to react the starting materials (XI) and (XII) in substantially equimolar proportions. The reaction is ordinarily carried out in a solvent, which is an organic solvent which does not interfere with the reaction. For example, there may commonly be employed methanol, ethanol, propanol or tetrahydrofuran. To allow the reaction to proceed more advantageously, a base may be incorporated in the solvent. As said base, there may be employed pyridine, triethylamine or N,N-dimethylaniline. Relative to the starting material (XI), the base is preferably added in a proportion of 100 to 300 percent by weight or, for better results, 100 to 200 percent by weight. Where R^2 is a hydrogen atom, no base need be externally added, for the compound (XII) as such acts as a base. The reaction proceeds smoothly at

from room temperature to reflux conditions. The reaction ordinarily goes to completion in tens of minutes to a few hours. Following the reaction, the protective group or groups are removed, if necessary, with or without prior isolation of the desired product. This removal reaction may be carried out in the same manner as mentioned hereinbefore. The isolation of the desired compound (IV) may also be carried out by the same isolation and purification procedures as those mentioned hereinbefore.

The compound (XIV) of this invention may be produced by reacting an α - oxyimino - β - keto - γ - halogenobutyric acid ester of the general formula:



(wherein X and $-\text{COOR}^{1'}$ are as defined hereinbefore) with a thiourea compound (XII). This reaction is conducted in an organic solvent such as ethanol or tetrahydrofuran. It is preferable to incorporate a base in the solvent. As said base, there is employed a tertiary base such as, for example, pyridine, triethylamine or N,N - dimethylaniline. Where $\text{R}^{2'}$ is a hydrogen atom, no additional base need be added, for the compound (XII) as such acts as a base. The reaction proceeds advantageously at from room temperature to reflux conditions. The resulting 2 - aminothiazole derivative (XIV) may be isolated and purified by procedures known *per se* but the reaction mixture may also be employed as the starting material according to this invention.

The desired compound (IV) thus obtained is an advantageous new intermediate for the production of penicillins and cephalosporins containing a 2 - aminothiazol - 4 - ylglucyl-amido group in their 6- and 7-positions, respectively, which have superior antibiotic potencies.

Some further details are now given of the reaction steps carried out to produce a compound (I) according to the invention.

Reaction of the compound (V) with (VI) is carried out as follows.

In the starting compounds (V), the symbol X means halogen such as chlorine, bromine, iodine or fluorine. When Y represents hydrogen, Z means an amino group which may be protected, such group being exemplified above. Alternatively, Y and Z together represent a group of the formula $=\text{NR}^3$, such group being also illustrated above.

The carboxyl group of the starting compound (V) may be protected with a protective group removable under mild conditions which will not destroy the thiazole ring, for example by acid or alkaline condition or reduction. Therefore, such protective groups may be

selected from those of carboxyl groups generally employed in peptide synthesis and are exemplified by alkali metals such as sodium and potassium, alkyl such as methyl, ethyl, propyl, isopropyl, butyl, sec - butyl, isobutyl and tert - butyl, substituted alkyl such as β - methylsulfonyl, ethyl, trichloroethyl and diphenylmethyl, aryl such as phenyl and tolyl, substituted aryl such as *p* - tert - butylphenyl and *p* - nitrophenyl, aralkyl such as benzyl, phenethyl and tolubenzyl, and substituted aralkyl such as *p* - methoxybenzyl and *p* - nitrobenzyl. In the present reaction, it is desirable to react substantially equivalent molar amounts of both the starting compounds (V) and (VI). The reaction is generally conducted in a solvent and such solvent may be selected from organic solvents which will not disturb the contemplated reaction. Thus, methanol, ethanol, propanol and tetrahydrofuran, for example, are suitably employed. The reaction is carried out smoothly at room temperature or under reflux conditions. The reaction is generally completed within one to several hours. The reaction may be carried out more smoothly by adding a base, such as N,N - dimethylaniline or triethylamine, to the reaction system. After the reaction is completed, the removal of the protecting group may be conducted directly in the reaction mixture or after isolation of the desired products, if desired. The purification of the products (I) may be carried out by conventional means such as solvent extraction, pH adjustment, crystallization, recrystallization, distillation, chromatography, or ion-exchange chromatography. When the starting compounds (VI) wherein R^{12} represents a lower alkoxy group are employed, there is obtained a contemplated compound (I) wherein R^1 is hydroxyl according to the present reaction.

Diazotization of the compounds (VII) may be carried out as follows.

The carboxylic group of the starting compounds (VII) employed in this reaction may be protected in a similar manner as mentioned for the above compounds (V). The reaction is generally conducted in a solvent, for example, water or a mixture of water and organic solvents which are readily miscible with water and do not disturb the present reaction, such as alcohols, e.g. methanol, ethanol, or ethers, e.g. tetrahydrofuran or dioxane. As the diazotization reagents, nitrous acid, alkyl nitrites, nitrogen dioxide and nitrosyl chloride are conveniently employed and, among them, acidified sodium nitrite and amyl nitrite are generally used. The reaction is generally conducted in the presence of an acid at a selected temperature within the range of 0 to 50°C for a selected time of one to several hours. The acid employed in the reaction is exemplified by hydrochloric acid, sulfuric acid, phosphoric acid, formic acid or acetic acid.

While α - oximino - 2 - substituted - thiazol - 4 - ylacetic acid derivatives (I) and (III) may occur theoretically as syn- and anti-isomers with respect to the oximino group, each of these isomers can be used similarly for the present reaction.

Reaction of the compounds (VIII) and a trihalogenoacetone may be carried out as follows.

The symbol R^{14} represents an amino group which may be protected as illustrated hereinbefore and, therefore, the compounds (VIII) are exemplified by N - (2,2,2 - trichloroethoxycarbonyl)thiourea, N - (t - butoxycarbonyl)thiourea, and N - (benzyloxycarbonyl)thiourea. As the trihalogenoacetone, there are generally used, for example, 1,1,3 - trichloroacetone or 1,1,3 - tribromoacetone.

The reaction may be carried out advantageously in a solvent. Any solvent which can dissolve both starting materials may be employed so far as it does not disturb the reaction, and more preferably it is exemplified by alcohols such as methanol, ethanol or propanol, ketones such as acetone or methyl ethyl ketone, ethers such as ether, tetrahydrofuran or dioxan, or a mixture thereof. The present reaction proceeds more smoothly in the presence of a base such as pyridine, picoline, quinoline, isoquinoline, triethylamine, tributylamine, N - methylpiperidine, N - methylmorpholine, N,N - dimethylaniline or N,N - diethylaniline. The reaction may proceed at room temperature and is accelerated by heating. Therefore, it is convenient to heat at about the boiling point of the solvent employed. When suitable conditions are selected in the present reaction, an intermediate, i.e. 4 - bromomethylthiazole, may be obtained in some cases.

The obtained compounds (IX) are subjected to an addition reaction with hydrogen cyanide to give so-called cyanhydrin compounds. For this purpose, cyanides such as sodium cyanide or potassium cyanide are generally reacted with the compounds (IX). The cyanhydrin compounds can be isolated as stable acyl derivatives by protecting with a suitable protective group, e.g. formyl or acetyl. An example of a desirable procedure is to react acetic anhydride with the cyanhydrin compounds in pyridine. The reaction to obtain the cyanhydrin compounds or their derivatives is preferably conducted in a solvent in the presence of a base. The solvent is desired to dissolve both the starting compounds and the base; and water or a mixture of water and an organic solvent miscible with water (e.g. methanol, ethanol, acetone or dimethylformamide) is generally employed. As the base employed, there may be conveniently used, for example, such a weak base as potassium dihydrogen phosphate, sodium hydrogen sulfite or triethylamine. The reaction is carried out advantageously under cool-

ing or in the neighbourhood of room temperature to avoid undesirable side reactions.

The reaction to obtain the cyanhydrin compounds as α - acetoxy - acetonitrile derivatives is usually conducted by reacting acetic anhydride with the former compounds in a solvent in the presence of base. In this reaction, any solvent, so far as it does not disturb the reaction, may be employed and there may be generally used, for example, an aprotic solvent such as chloroform, carbon tetrachloride, tetrahydrofuran, pyridine or dimethylformamide or a mixture thereof. Any base, so far as it does not disturb the present reaction, can be employed and preferable ones are organic tertiary bases such as pyridine, quinoline, isoquinoline, triethylamine or N,N - dimethylaniline. Among them, pyridine is most preferable because it also acts as a solvent. Acetic anhydride mentioned above is most preferable as the acylating agent, but other acylating agents, including acetyl chloride, may be also employed. The reaction proceeds smoothly under cooling, but, if desired, it may be conducted in the neighbourhood of room temperature.

The obtained cyanhydrin compounds in the form of their acyl derivatives are subjected to hydrolysis to give the desired compounds (II). The hydrolysis is carried out in a solvent in the presence of an acid or base. As the solvent, methanol or ethanol is generally used.

The reaction is conducted advantageously under cooling or in the neighbourhood of room temperature to avoid undesirable side reactions. In the reaction, an inorganic acid such as hydrochloric acid or sulfuric acid is preferably employed as the acid and sodium hydroxide or potassium hydroxide is preferably used as base.

While the thus obtained α - hydroxy- or α - amino - acetic acid derivative (II) is a racemic mixture, it can be resolved into optical active isomers, i.e. D-form and L-form, by *per se* known processes, for example, by converting them into a suitable diastereomer.

The invention is illustrated by the following Examples. Salts and reactive derivatives of the compounds can be prepared by methods known *per se*.

Example 1

(1) In 200 ml. of ethanol were dissolved 19.3 g. of ethyl α - oxyimino - β - oxo - γ - chlorobutyrate and 8.0 g. of thiourea, and the solution was refluxed for 2 hours. The ethanol was distilled off under reduced pressure and the residue was dissolved in 10% hydrochloric acid. To remove the unreacted ethyl α - oxyimino - β - oxo - γ - chlorobutyrate, the reaction mixture was washed twice with 200 ml. portions of ether, adjusted to pH 7.0 to 7.5 with sodium hydrogen carbonate and, then, extracted twice with 100 ml. portions of chloroform. The chloroform layer was

washed with water and dehydrated, followed by removal of the chloroform by distillation. The procedure provided ethyl 2 - aminothiazol - 4 - yl - α - oxyiminoacetate. Yield 6.43 g.; melting point: 137—138°C (decomp.).

Elemental analysis, for $C_7H_9O_3N_3S$

Calculated: C, 39.06; H, 4.21; N, 19.52.

Found: C, 39.64; H, 4.09; N, 19.02.

- 10 The infrared absorption spectrum of this product shows an absorption assignable to the oxime at 3430 cm^{-1} and an absorption assignable to the ester at 1710 cm^{-1} .

- 15 (2) In a mixture of 20 ml. 50% formic acid and 10 ml. methanol was dissolved 2.15 g. of the ethyl 2 - aminothiazol - 4 - yl - α - oxyiminoacetate prepared in (1). Under cooling with ice and stirring, 1.5 g. of zinc dust was added in small portions and the stirring was continued for 3 hours, at the end of which time the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure to obtain a crude solution containing 2 - aminothiazol - 4 - ylglycine ethyl ester.
- 20 The solution was directly passed through a column of 60 ml. Amberlite IR-120 (Amberlite is a Trade Mark), a strongly acidic ion exchange resin (H-form) and the formic acid was removed by repeated washing with water. Thereafter, elution was carried out with 10% aqueous ammonia and the eluate was concentrated under reduced pressure to recover 1.49 g. (86.4%) of 2 - aminothiazol - 4 - ylglycine. On recrystallization from aqueous ethanol, this compound had a melting point of 186—190°C (decomp.).

Elemental analysis, for $C_8H_{10}O_3N_3S \cdot \frac{1}{2}H_2O$

Calculated: C, 32.96; H, 4.43; N, 23.06.

Found: C, 32.94; H, 4.61; N, 22.22.

- 40 The nuclear magnetic resonance spectrum (60 Mc, in trifluoroacetic acid) of this compound showed a singlet assignable to the methine hydrogen in the side chain at 5.25 ppm and a singlet resonance line assignable to the thiazole ring hydrogens at 6.75 ppm. The compound gave a violet color reaction with the ninhydrin reagent.

Example 2

- 50 In 300 ml. of ethanol were dissolved 19.3 g. of thiourea and 53.5 g. of ethyl α - oxyimino - β - oxo - γ - chlorobutyrate and, after stirring at room temperature for 3 hours, the solution was concentrated under reduced pressure. The residue was dissolved by the addition of 200 ml. of water and the solution was washed twice with ether. Following the addition of 130 ml. 85% aqueous formic acid solution and 150 ml. ethanol and while the mixture was stirred under ice-cooling, 37 g. of zinc

dust was added in small portions. After all the indicated amount of zinc dust had been added, the reaction mixture was stirred at room temperature for 3 hours. The insoluble matter was filtered off and the filtrate as such was passed columnwise over Amberlite IR-120, a strongly acid ion exchange resin. The column was irrigated with water until the effluent was pH 7. Then, 10% aqueous ammonia was run down the column and the eluate was concentrated and lyophilized. The procedure provided 27.5 g. (63.6%) of 2 - aminothiazol - 4 - ylglycine.

In melting point and nuclear magnetic resonance spectrum, this product was found to be identical with the product according to Example 1.

Example 3

In a mixture of 10 ml. 50% aqueous formic acid solution and 5 ml. ethanol was dissolved 503 mg. of ethyl 2 - aminothiazol - 4 - yl - α - oxyiminoacetate hydrochloride and, under ice-cooling and stirring, 300 mg. of zinc dust was added in small portions. After the entire indicated amount of zinc dust had been added, the stirring was further continued for 3 hours, after which the ethanol was distilled off under reduced pressure and at a temperature not exceeding 30°C. The residue was adjusted to pH 7.5 with 1N NaOH and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dehydrated, followed by removal of ethyl acetate by distillation. The procedure provided 130 mg. (32.3%) of 2 - aminothiazol - 4 - ylglycine ethyl ester as crystals. The crystals colored and decomposed on contact with air. The nuclear magnetic resonance spectrum (60 Mc, in trifluoroacetic acid) of this product showed a triplet assignable to methyl protons at 1.04 ppm, a quartet due to methylene protons at 4.18 ppm, a singlet due to methylene protons at 5.35 ppm, and a singlet resonance line assignable to the thiazole 5 - hydrogen at 6.90 ppm. The mass spectrum of the compound gave a value of 201.0549 as compared to the theoretical value of 201.0571.

Example 4

In a mixture of 50 ml. ethanol and 20 ml. ether was dissolved 26.6 g. of ethyl α - acetamido - β - oxo - γ - bromobutyrate, followed by the addition of 9.14 g. of thiourea and 15 ml. of pyridine. The mixture was stirred at room temperature for 1 hour and, then, under reflux for 4 hours. The reaction mixture was concentrated and 50 ml. of ethyl acetate was added to the residue. The mixture was extracted with 3N HCl and the water layer was brought to pH 10 with 1N NaOH and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dehydrated and concentrated, followed by the addition of chloroform. The procedure provided 7.0 g. (34.5%) of crystalline ethyl 2 -

To a solution of 2.43 g. of ethyl α -ethoxy-

imino - 2 - aminothiazol - 4 - ylacetate hydrobromide in 25 ml. of anhydrous N,N - dimethylacetamide is added 1.43 g. of chloroacetyl chloride under cooling and stirring. The solution is stirred for 30 minutes under ice-cooling and then for 30 minutes at room temperature. To the reaction mixture is added 150 ml. of ethyl acetate and the mixture is repeatedly washed with saturated aq. NaCl solution. The ethyl acetate layer is dried over anhydrous magnesium sulfate, and subjected to distillation of the solvent under reduced pressure. To the residue is added water to precipitate solid material. The solid is collected by filtration and dried. The procedure gives 1.90 g. of ethyl α - ethoxyimino - 2 - (chloroacetamido)thiazol - 4 - ylacetate. Yield 79%.

NMR(ppm, 100 MHz, d_6 -DMSO): 1.24 and 1.27 (6H, two t, CH_3CH_2), 4.22 (4H, two q, CH_3CH_2), 4.30 (2H, S, $ClCH_2CO$), 7.99 (1H, S, thiazole ring proton).

Example 10

1.06 g. of ethyl α - ethoxyimino - 2 - (chloroacetylaminio)thiazol - 4 - ylacetate is suspended in a solution of 0.94 g. of potassium hydroxide in a mixture of 40 ml. of ethanol and 2 ml. of water and the suspension is stirred at room temperature to convert it to a solution, followed by further stirring for 45 minutes at room temperature. The reaction solution is subjected to distillation of ethanol under reduced pressure and the residue is adjusted to pH 2.0 with 1N hydrochloric acid under ice-cooling, to precipitate crystals. The crystals are filtered off, washed with water and dried. The procedure yields 0.88 g. of α - ethoxyimino - 2 - (chloroacetylaminio)thiazol - 4 - ylacetic acid. Yield 91%.

Analysis—Calcd. for $C_9H_{10}N_2O_5SCl$:

C, 37.05; H, 3.45; N, 14.41.

Found: C, 37.17; H, 3.44; N, 14.09.

NMR(ppm, 100 MHz, d_6 -DMSO): 1.28 (3H, t, CH_3CH_2), 4.22 (2H, q, CH_3CH_2), 4.32 (2H, S, $ClCH_2CO$), 8.00 (1H, S, thiazole ring proton).

Example 11

(1) To a solution of 5.03 g. of N - (β,β,β - trichloroethoxycarbonyl)thiourea and 5.32 g. of ethyl α - ethoxyimino - β - oxo - γ - bromobutyrate in 50 ml. of ethanol is added 3.03 g. of N,N - dimethylaniline and the mixture is heated for 2 hours in a water bath at 80°C. The reaction solution is subjected to distillation of ethanol and the residue is dissolved in ethyl acetate. The ethyl acetate solution is washed with dilute hydrochloric acid and then water, and dried, followed by the distillation of the solvent to give 7.85 g. of ethyl α - (2 - β,β,β - trichloroethoxy-

carbonylaminothiazol - 4 - yl) - α - ethoxyiminoacetate as an oil.

(2) To a solution of 2.00 g. of ethyl α - (2 - β,β,β - trichloroethoxycarbonylaminothiazol - 4 - yl) - α - ethoxyiminoacetate in 40 ml. of methanol is added 20 ml. of 1N sodium hydroxide. The solution is stirred for 2 hours at 50°C and concentrated. To the concentrate is added 50 ml. of water and the obtained solution is washed twice with ethyl acetate. The aqueous layer is adjusted to pH 2.0 with 3N hydrochloric acid to separate a white solid. The white solid is filtered off, washed with water and dried to give 1.40 g. of α - ethoxyimino - 2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - ylacetic acid. Yield 74.9%.

Analysis—Calcd. for $C_{19}H_{20}N_4O_5SCl_3$:

C, 30.75; H, 2.58; N, 10.76.

Found: C, 30.87; H, 2.41; N, 10.66.

NMR(ppm, 60 MHz, d_6 -DMSO): 1.13 (3H, t, CH_3CH_2), 4.06 (2H, q, CH_3CH_2), 4.90 (2H, S, Cl_3CCH_2O), 7.40 (1H, S, thiazole ring proton).

Example 12

To a solution of 27.3 g. of ethyl α - methoxyimino - β - oxobutyrate in 120 ml. of chloroform is dropwise added a solution of 25.3 g. of bromine in 30 ml. of chloroform over a period of 30 minutes. The solution is stirred for 1 hour at room temperature, and washed with dilute sodium bicarbonate aq. solution and water and dried. The dried solution is subjected to distillation of the solvent to give an oily crude product of ethyl α - methoxyimino - β - oxo - γ - bromobutyrate. The crude product is dissolved in 250 ml. of ethanol and 24 g. of thiourea is added thereto, followed by refluxing for 3 hours. After cooling, the precipitates are collected by filtration, washed with ethanol and then suspended in 300 ml. of a mixture of ethyl acetate and tetrahydrofuran (1:1). To the suspension is added 200 ml. of 10% sodium bicarbonate aq. solution and the mixture is thoroughly shaken. The organic layer is dried and subjected to distillation of the solvent to give crystals, followed by washing with ether. The procedure gives 16.86 g. of ethyl α - methoxyimino - α - (2 - aminothiazol - 4 - yl)acetate. Melting point: 112—113°C.

Analysis—Calcd. for $C_{11}H_{11}N_3O_5S$:

C, 41.91; H, 4.84.

Found: C, 41.20; H, 4.70.

NMR(ppm, 60 MHz, $CDCl_3$): 4.04 (3H, S, OCH_3), 7.44 (1H, S, thiazole ring proton).

Example 13

To a solution of 10 g. of ethyl α - methoxy-

imino - α - (2 - aminothiazol - 4 - yl)acetate in 100 ml. of dimethylacetamide is dropwise added 5.91 g. of chloroacetyl chloride under ice-cooling. After stirring for 1 hour at room temperature, the reaction mixture is poured into ice-water and the resultant solution is extracted with ethyl acetate. The organic layer is washed and dried, followed by distillation of solvent to give 12.66 g. of ethyl α - methoxyimino - α - [2 - (chloroacetamido)thiazol - 4 - yl]acetate as crystals. Melting point: 81–82°C.

Analysis—Calcd. for $C_{10}H_{12}N_2O_4SCl$:

C, 39.29; H, 3.96.

Found: C, 38.74; H, 3.58.

NMR(ppm, 60 MHz, $CDCl_3$): 4.10 (3H, S, OCH_3), 4.24 (2H, S, $ClCH_2CO$ —), 7.94 (1H, S, thiazole ring proton).

Example 14

12.66 g. of ethyl α - methoxyimino - α - [2 - (chloroacetamido)thiazol - 4 - yl]acetate is added to a solution of 11.74 g. of potassium hydroxide in a mixture of 25 ml. of water and 500 ml. of ethanol. After stirring for 20 minutes at room temperature, the reaction solution is subjected to distillation of ethanol under reduced pressure. The residue is added to water, and the resultant solution is made acidic with addition of N hydrochloric acid, followed by separating the insoluble materials by filtration. The procedure yields 10.54 g. of α - methoxyimino - α - [2 - (chloroacetamido)thiazol - 4 - yl]acetic acid. Melting point: 182–183°C.

Analysis—Calcd. for $C_9H_{10}N_2O_4SCl$:

C, 34.60; H, 2.90; N, 15.13.

Found: C, 34.53; H, 3.00; N, 14.80.

NMR(ppm, 60 MHz, d_6 -DMSO): 4.00 (3H, S, OCH_3), 4.38 (2H, S, $ClCH_2CO$), 8.00 (1H, S, thiazole ring proton).

Example 15

A solution of 10.45 g. of α - ethoxyimino - α - [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetic acid ethyl ester in a mixture of 10% hydrochloric acid and ethanol is catalytically hydrogenated over 8.0 g. of 5% palladium on charcoal at room temperature under atmospheric pressure. After the absorption of two equivalents of hydrogen, the catalyst in the reaction mixture is filtered off and the filtrate is concentrated to dryness under reduced pressure. By the procedure, 7.43 g. of α - amino - α - [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetic acid ethyl ester hydrochloric acid salt is obtained (yield, 72%). This product is suspended in ethyl acetate and the obtained suspension is washed with saturated sodium bicarbonate aq. solution, washed with water

and dried over anhydrous magnesium sulfate. The oily product obtained by the distillation of the solvent is dissolved in 60 ml. of N,N - dimethylformamide and, to the solution is added 4.2 g. of tetramethylguanidine and then 3.94 g. of t - butyloxycarbonylazide, followed by stirring for 15 hours at room temperature. The reaction mixture is poured into water and extracted with ethyl acetate. The organic layer is washed with 1N hydrochloric acid and then saturated aq. NaCl solution and dried over anhydrous magnesium sulfate. The oily product obtained by the distillation of the solvent is purified by a column chromatography in a column packed with silica gel. The procedure gives 4.06 g. of α - t - butyloxycarbonylamino - α - [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetic acid ethyl ester (yield, 46.5%). Melting point: 94–95°C.

Analysis—Calcd. for $C_{15}H_{20}N_2O_6SCl_3$:

C, 37.79; H, 4.23; N, 8.81.

Found: C, 37.64; H, 4.28; N, 8.73.

Example 16

To a solution of 2.80 g. of α - t - butyloxycarbonylamino - α - [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetic acid ethyl ester in 60 ml. of 90% formic acid is added 2.80 g. of zinc dust under cooling and stirring. The mixture is stirred for 1 hour and zinc dust is filtered off. The filtrate is poured into water and the resultant solution is extracted with ethyl acetate. The organic layer is washed with saturated aqueous sodium bicarbonate solution and then water, and dried over anhydrous magnesium sulfate. The distillation of the solvent gives 1.26 g. (yield, 71.2%) of α - t - butyloxycarbonylamino - α - (2 - aminothiazol - 4 - yl)acetic acid ethyl ester as crystals. Melting point: 143–144°C.

Analysis—Calcd. for $C_{12}H_{14}N_2O_4S$:

C, 47.83; H, 6.35; N, 13.95.

Found: C, 47.79; H, 6.27; N, 13.70.

Example 17

To a solution of 1.26 g. of α - t - butyloxycarbonylamino - α - (2 - aminothiazol - 4 - yl)acetic acid ethyl ester in 5 ml. of N,N - dimethylacetamide is added 708 mg. of chloroacetyl chloride under stirring. After stirring for 1 hour at room temperature, the reaction solution is poured into water and extracted with ethyl acetate. The organic layer is washed with saturated aqueous sodium bicarbonate solution and then water and dried over anhydrous magnesium sulfate. The distillation of the solvent gives 1.435 g. of α - t - butyloxycarbonylamino - α - [2 - (chloroacetamido)thiazol - 4 - yl]acetic acid ethyl ester as crystals (yield, 90.8%). Melting point: 192–193°C.

Analysis—Calcd. for $C_{14}H_{20}ClN_2O_5S$:
 C, 44.50; H, 5.34; N, 11.12.
 Found: C, 44.87; H, 5.55; N, 10.94.

acetamidothiazol - 4 - yl - N - chloroacetyl-
 glycine as colorless crystals. Melting point:
 184—186°C.

Example 18

5 To a solution of 920 mg. of α - t -
 butyloxycarbonylamino - α - [2 - (chloro-
 acetamido)thiazol - 4 - yl]acetic acid ethyl
 ester in 20 ml. of ethanol is added 1.4 ml. of
 10 an aqueous solution containing 681 mg. of
 potassium hydroxide and the mixture is
 stirred for 15 minutes at room temperature.
 The reaction solution is concentrated to dry-
 ness under reduced pressure and the residue
 15 is dissolved in water. The aqueous solution is
 adjusted to pH 2.0 with 1N hydrochloric acid
 and extracted with ethyl acetate. The organic
 layer is washed with water and dried over
 anhydrous magnesium sulfate. The solvent is
 20 distilled to obtain 690 mg of α - t - butyloxy-
 carbonylamino - α - [2 - (chloroacetamino)-
 thiazol - 4 - yl]acetic acid as crystals (yield,
 81%). Melting point: 169—170°C (dec.).

Analysis—Calcd. for $C_{12}H_{16}ClN_2O_5S$:
 C, 41.21; H, 4.61; N, 12.01.
 25 Found: C, 41.40; H, 4.68; N, 11.74.

Example 19

To a solution of 11 g. of 2 - aminothiazol -
 4 - ylglycine ethyl ester in 100 ml. of di-
 methylacetamide is added dropwise 17 g. of
 30 chloroacetyl chloride for 40 minutes under
 ice-cooling and the mixture is stirred at room
 temperature overnight. To the reaction mix-
 ture is added 200 ml. of ice-water and the
 mixture is extracted with ethyl acetate. The
 35 organic layer is washed with water, dried and
 concentrated to obtain 14.8 g. of 2 - chloro-
 acetamidothiazol - 4 - yl - N - chloroacetyl-
 glycine ethyl ester as colorless crystals. Melting
 point: 102.5—103.5°C.

40 NMR(ppm, 60 MHz, $CDCl_3$): 4.16 (2H, S,
 $ClCH_2CO$), 4.32 (2H, S, $ClCH_2CO$),

5.74 (1H, d, $-CH-COOH$),
 |
 NH

7.14 (1H, S, thiazole ring proton).

Example 20

45 To a solution of 3.54 g. of 2 - chloroacet-
 amidothiazol - 4 - yl - N - chloroacetyl-glycine
 ethyl ester in 30 ml. of ethanol is added
 dropwise a solution of 1.68 g. of potassium
 50 hydroxide in 15 ml. of water under ice-cool-
 ing, followed by stirring for 15 minutes.
 Ethanol is distilled off under reduced pressure
 and the residue is made acidic with 10%
 hydrochloric acid, followed by extraction with
 ethyl acetate. The ethyl acetate layer is
 55 washed with water and dried. The distillation
 of ethyl acetate gives 2.38 g. of 2 - chloro-

NMR(ppm, 60 MHz, d_6 -DMSO): 4.36 (2H,
 S, $ClCH_2CO$), 4.58 (2H, S, $ClCH_2CO$),

5.66 (1H, d, $-CH-COO$),
 |
 NH

7.40 (1H, S, thiazole ring proton).

Example 21

To a solution of 2.2 g. of ethyl α - 65
 methoxyimino - β - oxo - γ - bromobutyrate
 in 40 ml. of ethanol are added 1.22 g. of
 dimethylaniline and 2.2 g. of N - (β,β,β -
 trichloroethoxycarbonyl)thiourea. The mix-
 70 ture is heated for 1.5 hours under reflux and
 concentrated under reduced pressure. The
 concentrate of the reaction mixture is
 recrystallized from ligroin to give ethyl α -
 methoxyimino - [2 - (β,β,β - trichloroethoxy-
 carbonylamino)thiazol - 4 - yl]acetate as
 75 crystals. 1.84 g. Melting point: 125—128°C.

Analysis—Calcd. for $C_{11}H_{12}O_5N_2SCl_3$:
 C, 32.65; H, 2.99; N, 10.38.
 Found: C, 32.81; H, 3.14; N, 10.19.

NMR(ppm, 100 MHz, $CDCl_3$): 7.15 (1H, 80
 s, 5-H).

Example 22

To a solution of 8.1 g. of ethyl α -
 methoxyimino - [2 - (β,β,β - trichloroethoxy-
 carbonylamino)thiazol - 4 - yl]acetate in 85
 50 ml. of ethanol is added a solution of 11.2 g.
 of KOH in a mixture of 30 ml. of water and
 150 ml. of ethanol. The whole mixture is
 stirred at room temperature for 1 hour, and
 then concentrated under reduced pressure. 90
 The residue is extracted with ethyl acetate.
 The water layer is made acidic with 10% aq.
 HCl and the separated solid is collected.
 Recrystallization of the solid from aq.
 methanol gives α - methoxyimino - [2 -
 95 (β,β,β - trichloroethoxycarbonylamino)-
 thiazol - 4 - yl]acetic acid. 4.1 g. Melting
 point: 162—163°C.

Analysis—Calcd. for $C_9H_{10}O_5N_2SCl_3$:
 C, 28.70; H, 2.14; N, 11.16. 100
 Found: C, 28.64; H, 2.11; N, 11.06.

NMR(ppm, 100 MHz, $CDCl_3 + d_6$ -DMSO):
 7.26 (1H, s, 5-H).

Example 23

Ethyl α - methoxyimino - [2 - (β,β,β - 105
 trichloroethoxycarbonylamino)thiazol - 4 -
 yl]acetate (2.02 g.) dissolved in 150 ml. of
 ethanol containing 10% HCl is hydrogenated
 in the presence of 2.0 g. of 5% Pd/carbon.
 After 240 ml. of hydrogen is absorbed, the 110

reaction mixture is filtered and the filtrate is condensed under reduced pressure. The residue is washed with ether and suspended in 70 ml. of ethyl acetate followed by the addition of 20 ml. of 5% aq. NaHCO_3 . The ethyl acetate layer is separated, washed, dried and condensed to give [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]glycine ethyl ester. 1.22 g.

Analysis—Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_4\text{N}_2\text{SCl}_3$:
C, 31.89; H, 3.21; N, 11.16.
Found: C, 31.91; H, 3.00; N, 10.63.

NMR(ppm, 100 MHz, CF_3COOD): 5.82 (1H, s, $>\text{CH}-\text{COOC}_2\text{H}_5$), 7.74 (1H, s, 5-H).

Example 24

To a solution of 238 mg. of ethyl α - oximino - β - oxo - γ - bromobutyrate in 10 ml. of ethanol is added 251 mg. of N - (β,β,β - trichloroethoxycarbonyl)thiourea and the mixture is heated under reflux for 6 hours. After cooling, 50 ml. of chloroform is added and the organic solution is washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by chromatographic purification on silica gel affords 164 mg. of ethyl α - oximino - α - [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetate.

Analysis—Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_5\text{SCl}_3$:
C, 30.74; H, 2.58; N, 10.75; Cl, 27.23.
Found: C, 30.95; H, 2.51; N, 10.75; Cl, 27.02.

NMR(ppm, 100 MHz, CDCl_3): 1.35 (3H, t, CH_3CH_2), 4.36 (2H, q, CH_2CH_2), 4.87 (2H, s, Cl_3CCH_2), 7.94 (1H, s, thiazole ring proton).

Example 25

A solution of 2.0 g. of ethyl α - oximino - α - [2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetate in 50 ml. of 10% HCl-ethanol is hydrogenated over 0.5 g. of 5% palladium-on-charcoal under shaking. The reaction stops when 90 ml. of hydrogen is absorbed. Additional 1.5 g. of the catalyst is added and 170 ml. of hydrogen is absorbed. Insoluble material is filtered off and the filtrate is concentrated under reduced pressure. The residue is washed with ether, and separated. The separated solid is dissolved in 5 ml. of water and neutralized with 10% sodium hydrogen carbonate aq. solution, and then extracted with chloroform. The extract is washed with water, drying over anhydrous magnesium sulfate and subjected to the evaporation of the solvent. The resultant residue is followed by chromatographic purification on silica gel column to afford 560 mg. of 2 - (β,β,β - trichloroethoxy-

carbonylamino)thiazol - 4 - ylglycine ethyl ester.

Analysis—Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4\text{SCl}_3$:
C, 31.89; H, 3.21; N, 11.16.
Found: C, 31.91; H, 3.00; N, 10.63.

NMR(ppm, 100 MHz, $\text{CF}_3\text{CO}_2\text{D}$): 1.37 (3H, t, CH_3CH_2), 4.47 (2H, q, CH_2CH_2), 4.98 (2H, s, Cl_3CCH_2), 5.82 (1H, s, CH), 7.74 (1H, s, thiazole ring proton).

Example 26

To a solution of 3.40 g. of 2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - ylglycine ethyl ester in 50 ml. of chloroform are added gradually 1.2 g. of triethylamine and 2.50 g. of β,β,β - trichloroethoxycarbonyl chloride under stirring at room temperature. After 30 minutes stirring, 100 ml. of chloroform is added to the mixture and the obtained organic solution is washed with saturated NaCl aq. solution, 1N - hydrochloric acid and then with water, and dried over anhydrous magnesium sulfate. After the evaporation of the solvent n - hexane is added to the residue to afford crude product. The crude product is recrystallized from a mixture of ligroin and n - hexane to give 4.11 g. of 2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl - N - (β,β,β - trichloroethoxycarbonyl)glycine ethyl ester. Yield 82%.

Analysis—Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_6\text{SCl}_3$:
C, 28.28; H, 2.37; N, 7.61.
Found: C, 28.39; H, 2.38; N, 7.71.

NMR(ppm, 100 MHz, CDCl_3): 1.21 (3H, t, CH_3CH_2), 4.60 (2H, q, CH_2CH_2), 4.83 and 4.86 (4H, two s, Cl_3CCH_2), 5.60 (1H, d, CH), 6.98 (1H, s, thiazole ring proton), 7.38 (1H, d, α -NH).

Example 27

To a solution of 3.82 g. of 2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl - N - (β,β,β - trichloroethoxycarbonyl)glycine ethyl ester in 150 ml. of ethanol is added a solution of 1.94 g. of potassium hydroxide in 10 ml. of water while stirring at room temperature. After 30 minutes stirring, the solution is concentrated under reduced pressure and 50 ml. of water is added to the residue. The aqueous solution is washed with ethyl acetate, adjusted to pH 2.0 with 1N - hydrochloric acid and extracted twice each with 70 ml. of ethyl acetate. The combined extracts are washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. n - Hexane is added to the residue to separate crude material. The crude material is recrystallized from a mixture of ethyl acetate and ligroin to afford 1.83 g. of 2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 -

yl - N - (β,β,β - trichloroethoxycarbonyl)-glycine. Yield 50%.

NMR(ppm, 100 MHz, CDCl_3): 4.80 (4H, s, Cl_3CCH_2), 4.65 (1H, s, 2-NH), 5.48 (1H, broad d, CH), 6.14 (1H, broad d, α -NH), 6.95 (1H, s, thiazole ring proton).

Example 28

To a suspension of 3.46 g. of 2 - aminothiazol - 4 - ylglycine in 100 ml. of N,N - dimethylacetamide is added dropwise 12.66 g. of β,β,β - trichloroethoxycarbonyl chloride while stirring for 30 minutes at room temperature. After further 30 minutes stirring, 250 ml. of ethyl acetate is added to the reaction mixture and the resulting solution is washed with 70 ml. of 1N - hydrochloric acid. The ethyl acetate is separated and extracted 3 times with 50 ml. of 3% aq. potassium hydroxide solution. The combined aqueous extracts are washed with ethyl acetate, adjusted to pH 2.0 with 1N - hydrochloric acid and extracted 3 times each with 100 ml. of ethyl acetate. The combined extracts are washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. n - Hexane is added to the oily residue to precipitate crude material. Crude material is separated and recrystallized from a mixture of ethyl acetate and ligroin to afford 510 mg. of 2 - (β,β,β - trichloroethoxycarbonylamino)thiazol - 4 - yl - N - (β,β,β - trichloroethoxycarbonyl)-glycine. This product is identical with the compound obtained in Example 27 in all respects.

Example 29

A solution of 10.0 g. of N - (β,β,β - trichloroethoxycarbonyl)thiourea, 12.0 g. of 1,1,3 - tribromoacetone and 5.0 g. of dimethylaniline in 100 ml. of ethanol is heated under reflux for 2 hours. After cooling, ethanol is removed under reduced pressure, and the oily residue is dissolved in ethyl acetate. The ethyl acetate layer is washed with water and dried over MgSO_4 . Ethyl acetate is removed under reduced pressure and the oily residue is dissolved in a small quantity of chloroform. From the solution which is allowed to stand at room temperature is obtained 2 - (β,β,β - trichloroethoxycarbonyl)amino - 4 - formylthiazole in crystalline form. 5.0 g. Melting point: 188—190°C.

Analysis—Calcd. for $\text{C}_7\text{H}_6\text{O}_3\text{N}_2\text{SCl}_3$:
C, 27.69; H, 1.66; N, 9.23.
Found: C, 27.87; H, 1.69; N, 9.01.

NMR(ppm, 100 MHz, CDCl_3 -d₆, DMSO): 5.05 (2H, s, Cl_3CCH_2 —), 8.05 (1H, s, 5-H), 9.80 (1H, s, CHO).

Example 30

To a mixture of 1.0 g. of 2 - (β,β,β -

trichloroethoxycarbonyl)amino - 4 - formylthiazole, 0.87 g. of KH_2PO_4 , 6 ml. of water and 4 ml. of dimethylformamide is added 0.33 g. of KCN at room temperature and the mixture is stirred for 30 minutes. The reaction mixture is extracted with ethyl acetate and the ethyl acetate layer is washed with water and dried. Evaporation of ethyl acetate gives α - hydroxy - [2 - (β,β,β - trichloroethoxycarbonyl)aminothiazol - 4 - yl]acetonitrile, 1.127 g.

NMR(ppm, 100 MHz, CDCl_3): 4.90 (2H, s, Cl_3CCH_2 —), 5.70 (1H, s, —CHCN), 7.90 (1H, s, 5H).

Example 31

To a solution of 1.10 g. of α - hydroxy - [2 - (β,β,β - trichloroethoxycarbonyl)aminothiazol - 4 - yl]acetonitrile in 1 ml. of pyridine is added 2.5 ml. of acetic anhydride under ice-cooling and the mixture is stirred for 1 hour. To the mixture is added ether and water and the organic layer is washed with aq. NaHCO_3 and further water in this order. Evaporation of ether gives α - acetoxy - [2 - (β,β,β - trichloroethoxycarbonyl)aminothiazol - 4 - yl]acetonitrile. 1.3 g.

NMR(ppm, 100 MHz, CDCl_3): 2.20 (3H, s, COCH_3), 5.00 (2H, s, Cl_3CCH_2 —), 6.60 (1H, s, >CHCN), 7.30 (1H, s, 5-H).

Example 32

Into a solution of 1.30 g. of α - acetoxy - [2 - (β,β,β - trichloroethoxycarbonyl)aminothiazol - 4 - yl]acetonitrile in 10 ml. of methanol is bubbled gaseous hydrochloric acid for 10 minutes under ice-cooling, and the mixture is kept standing at room temperature for 1 hour. After evaporation of methanol there is added 40 ml. of 50% aq. methanol to the residue and the resulting mixture is stirred for 1 hour. To this reaction mixture is added 1.0 g. of NaOH and the resulting mixture is stirred for a further hour. Methanol is removed under reduced pressure and the residue is extracted with ethyl acetate after being made acidic with N-HCl. The ethyl acetate layer is washed with water and dried. Ethyl acetate is removed under reduced pressure to obtain α - hydroxy - [2 - (β,β,β - trichloroethoxycarbonyl)amino]thiazol - 4 - yl - acetic acid. 0.996 g. Melting point: 135—136°C.

Analysis—Calcd. for $\text{C}_7\text{H}_6\text{O}_3\text{N}_2\text{SCl}_3$:
C, 27.48; H, 2.02; N, 8.01.
Found: C, 27.72; H, 2.05; N, 8.08.

NMR(ppm, 100 MHz, CDCl_3): 4.90 (2H, s, Cl_3CCH_2 —), 5.40 (1H, s, >CH—COOH), 7.10 (1H, s, 5-H).

Example 33

To a solution of 21.43 g. of ethyl α -

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ethoxyimino - β - oxo - γ - bromobutyrate in 80 ml. of ethanol is added 8.81 g. of methyl thionocarbamate and the mixture is heated under reflux for 1.5 hours. After cooling ethanol is removed under reduced pressure and the oily residue is dissolved in chloroform. The chloroform solution is washed, dried, and condensed. The condensate is purified by silica gel chromatography to give 11.9 g. of ethyl α - ethoxyimino - (2 - hydroxythiazol - 4 - yl)acetate. Melting point: 54–55°C.

Analysis—Calcd. for $C_8H_{12}O_4N_2S$:

C, 44.25; H, 4.95; N, 11.47.

Found: C, 44.54; H, 5.04; N, 11.53.

NMR(ppm, 100 MHz, $CDCl_3$): 6.33 (1H, s, 5-H).

Example 34

To a solution of 10 g. of ethyl α - ethoxyimino - (2 - hydroxythiazol - 4 - yl)acetate in 30 ml. of ethanol is added a solution of 11.47 g. of KOH in 50 ml. of water at room temperature and the mixture is stirred for 25 minutes. The reaction mixture is condensed under reduced pressure and is made acidic with 10% aq. HCl. An ethyl acetate extract of the reaction mixture is extracted with 10% aq. $NaHCO_3$. The aqueous layer is then made acidic with 10% aq. HCl and extracted again with ethyl acetate. From the ethyl acetate extract, after being washed, dried and condensed, is obtained a crystalline substance. Recrystallization from benzene - ethanol gives α - ethoxyimino - (2 - hydroxythiazol - 4 - yl)acetic acid. 7.5 g. Melting point: 131.5°C (dec.).

Analysis—Calcd. for $C_7H_8O_4N_2S$:

C, 38.88; H, 3.72; N, 12.95.

Found: C, 38.65; H, 3.85; N, 13.06.

NMR(ppm, 100 MHz, d_6 -DMSO): 6.64 (1H, s, 5-H).

Example 35

To a mixture of 1 g. of α - ethoxyimino - (2 - hydroxythiazol - 4 - yl)acetic acid, 10 ml. of 50% aq. formic acid and 5 ml. of methanol is added gradually 0.9 g. of zinc dust under ice-cooling. The mixture is stirred for 1 hour in this state and then for 30 minutes at room temperature. The reaction mixture is filtered and the filtrate is passed through a column packed with ion-exchange resin [Amberlite IR-120(H)] to give purified 2 - hydroxythiazol - 4 - ylglycine.

Analysis—Calcd. for $C_6H_8O_3N_2S$:

N, 16.08.

Found: N, 15.96.

NMR(ppm, 100 MHz, CF_3COOD): 5.56 (1H, s, $>CH-COOH$), 6.91 (1H, s, 5-H).

Example 36

To a mixture of 40 ml. of concentrated HCl and 100 ml. of water is dissolved under ice-cooling 8.8 g. of ethyl α - oxyimino - (2 - aminothiazol - 4 - yl)acetate. A solution of 2.8 g. of $NaNO_2$ in 20 ml. of water is added dropwise to this solution in a period of 20 minutes. After being stirred for 2.5 hours under ice-cooling the reaction mixture is extracted with 200 ml. of ethyl acetate. The extract is washed with water and dehydrated. The ethyl acetate is distilled off and the resultant oil is purified by silica gel chromatography to give ethyl α - oxyimino - (2 - hydroxythiazol - 4 - yl)acetate.

NMR(ppm, 100 MHz, $CDCl_3$): 1.37 (3H, t, CH_3CH_2), 4.36 (2H, q, CH_2CH_3), 8.02 (1H, s, 5-H).

Example 37

To a solution of 1.3 g. of ethyl α - oxyimino - (2 - hydroxythiazol - 4 - yl)acetate in 5 ml. of ethanol is added under ice-cooling 30 ml. of 50% aq. formic acid. Zinc dust (1.17 g.) is added gradually to this solution in a period of 5 minutes under stirring. The reaction mixture is stirred for 2 hours under ice-cooling and filtered. The filtrate is condensed under reduced pressure and the residue is poured into 10 ml. of water. The water layer is neutralized with 10% aq. $NaHCO_3$ and then extracted with ethyl acetate. The extract is washed with water and dehydrated. The ethyl acetate is distilled off and the resultant oil is purified by silica gel chromatography to give 2 - hydroxythiazol - 4 - ylglycine ethyl ester.

NMR(ppm, 100 MHz, $CDCl_3$): 1.22 (3H, t, $-CH_2CH_3$), 4.27 (2H, q, $-CH_2CH_3$), 4.65 (1H, s, $>CH-COOC_2H_5$), 7.14 (1H, s, 5-H).

The ester is acylated with β,β,β - trichloroethyl chloroformate in CH_2Cl_2 in the presence of triethylamine to give ethyl α - (β,β,β - trichloroethoxycarbonylamino) - (2 - hydroxythiazol - 4 - yl)acetate.

Analysis—Calcd. for $C_{10}H_{11}O_5N_2SCl_3$:

N, 7.41.

Found: N, 7.39.

NMR(ppm, 100 MHz, $CDCl_3$): 1.26 (3H, t, $-CH_2CH_3$), 4.22 (2H, q, $-CH_2CH_3$), 4.70 (2H, s, Cl_3CCH_2), 5.42 (1H, d, $>CH-COOC_2H_5$), 7.24 (1H, s, 5-H).

Example 38

To a solution of 1.93 g. of ethyl α - oxyimino - β - oxo - γ - chlorobutyrate in 10 ml. of ethanol is added 1.27 g. of ethyl thionocarbamate and the mixture is heated for 2 hours under reflux. After cooling ethanol is

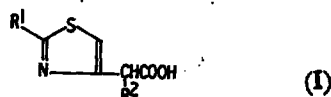
evaporated and then the remaining oily substance is purified by means of silica gel chromatography to give ethyl α -oxyimino-(2-hydroxythiazol-4-yl)acetate. The ester is identical with the substance obtained in Example 36 in all respects.

Example 39

To a solution of 2.65 g. of ethyl α -acetamido- β -oxo- γ -bromobutyrate in 10 ml. of ethanol is added 1.09 g. of methyl thionocarbamate. The mixture is heated for 1.5 hours under reflux and concentrated under reduced pressure. The concentrate is dissolved in chloroform. The chloroform layer is washed, dried and concentrated to give ethyl α -acetamido-(2-hydroxythiazol-4-yl)acetate as an oily material. This ester (2.0 g.) is dissolved in 10 ml. of methanol and to this is added a solution of 3.09 g. of $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ in 50 ml. of water and the whole mixture is stirred at 70°C for 3 hours. After cooling, gaseous CO_2 is bubbled into the reaction mixture to cause precipitation of BaCO_3 . The BaCO_3 thus precipitated is filtered off and the filtrate is passed through a column packed with ion-exchange resin [Amberlite IR-120(H)] to give purified 2-hydroxythiazol-4-ylglycine. This substance is identical with the sample obtained in Example 35 in all respects.

WHAT WE CLAIM IS:—

1. A thiazole compound of the general formula:



wherein R^1 represents an amino or hydroxyl group which may be protected, and R^2 represents an amino group which may be protected or a hydroxyl group, or

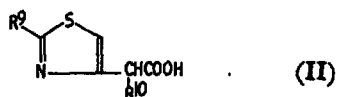


represents a group of the formula



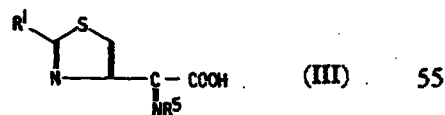
where R^5 represents a hydroxyl group which may be protected, provided that R^2 does not represent a hydroxyl group when R^1 represents an optionally protected hydroxyl group, or a salt or reactive derivative thereof.

2. A compound of the formula:



wherein each of R^9 and R^{10} independently represents an amino or hydroxyl group, providing R^9 and R^{10} do not both represent a hydroxyl group, or a salt or reactive derivative thereof.

3. A compound of the formula:



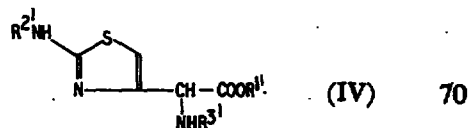
wherein R^1 represents an amino or hydroxyl group which may be protected and R^5 represents a hydroxyl group which may be protected, or a salt or reactive derivative thereof.

4. Ethyl α -acetamido- α -(2-(β,β,β -trichloroethoxy-carbonylamino)thiazol-4-yl)acetate.

5. α -Chloroacetamido- α -(2-chloroacetamidothiazol-4-yl)acetic acid.

6. α -Methoxyimino- α -(2-(β,β,β -trichloroethoxycarbonylamino)thiazol-4-yl)acetic acid.

7. A 2-aminothiazol-4-ylglycine derivative of general formula (IV):



wherein $\text{R}^{2'}\text{NH}$ and $\text{NHR}^{3'}$ are optionally protected amino groups and $\text{COOR}^{1'}$ is an optionally protected carboxyl group.

8. Ethyl α -methoxyimino- α -(2-aminothiazol-4-yl)acetate.

9. Ethyl α -methoxyimino- α -(2-(chloroacetamido)thiazol-4-yl)acetate.

10. α -Methoxyimino- α -(2-(chloroacetamido)thiazol-4-yl)acetic acid.

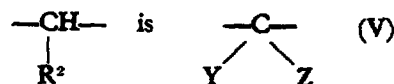
11. Ethyl α -methoxyimino- α -(2-(β,β,β -trichloroethoxycarbonylamino)thiazol-4-yl)acetate.

12. A compound as claimed in claim 3, wherein R^5 represents a methoxy group.

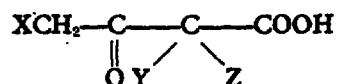
13. A compound as claimed in claim 3 wherein R^1 represents an ethoxy group.

14. A process for preparing a compound of the formula (I) as defined in claim 1, which comprises

(1) in the case where R^1 is an amino or hydroxyl group which may be protected and



where Y and Z are defined below, reacting a compound of the formula:





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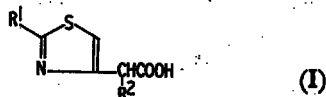
evaporated and then the remaining oily substance is purified by means of silica gel chromatography to give ethyl α - oxyimino - (2 - hydroxythiazol - 4 - yl)acetate. The ester is identical with the substance obtained in Example 36 in all respects.

Example 39

To a solution of 2.65 g. of ethyl α - acetamido - β - oxo - γ - bromobutyrate in 10 ml. of ethanol is added 1.09 g. of methyl thionocarbamate. The mixture is heated for 1.5 hours under reflux and concentrated under reduced pressure. The concentrate is dissolved in chloroform. The chloroform layer is washed, dried and concentrated to give ethyl α - acetamido - (2 - hydroxythiazol - 4 - yl)acetate as an oily material. This ester (2.0 g.) is dissolved in 10 ml. of methanol and to this is added a solution of 3.09 g. of $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ in 50 ml. of water and the whole mixture is stirred at 70°C for 3 hours. After cooling, gaseous CO_2 is bubbled into the reaction mixture to cause precipitation of BaCO_3 . The BaCO_3 thus precipitated is filtered off and the filtrate is passed through a column packed with ion-exchange resin [Amberlite IR-120(H)] to give purified 2 - hydroxythiazol - 4 - ylglycine. This substance is identical with the sample obtained in Example 35 in all respects.

WHAT WE CLAIM IS:—

1. A thiazole compound of the general formula:



wherein R^1 represents an amino or hydroxyl group which may be protected, and R^2 represents an amino group which may be protected or a hydroxyl group, or

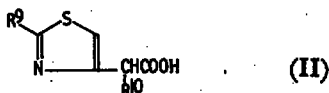


represents a group of the formula



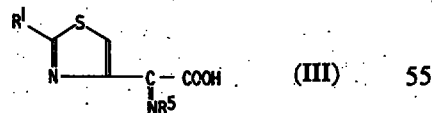
where R^5 represents a hydroxyl group which may be protected, provided that R^2 does not represent a hydroxyl group when R^1 represents an optionally protected hydroxyl group, or a salt or reactive derivative thereof.

2. A compound of the formula:



wherein each of R^9 and R^{10} independently represents an amino or hydroxyl group, providing R^9 and R^{10} do not both represent a hydroxyl group, or a salt or reactive derivative thereof.

3. A compound of the formula:



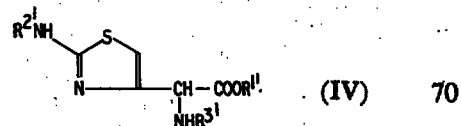
wherein R^1 represents an amino or hydroxyl group which may be protected and R^5 represents a hydroxyl group which may be protected, or a salt or reactive derivative thereof.

4. Ethyl α - acetamido - α - [2 - (β, β, β - trichloroethoxy - carbonylamino)thiazol - 4 - yl]acetate.

5. α - Chloroacetamido - α - (2 - chloroacetamidothiazol - 4 - yl)acetic acid.

6. α - Methoxyimino - α - [2 - (β, β, β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetic acid.

7. A 2 - aminothiazol - 4 - ylglycine derivative of general formula (IV):



wherein R^2NH and NHR^3 are optionally protected amino groups and COOR^1 is an optionally protected carboxyl group.

8. Ethyl α - methoxyimino - α - (2 - aminothiazol - 4 - yl)acetate.

9. Ethyl α - methoxyimino - α - [2 - (chloroacetamido)thiazol - 4 - yl]acetate.

10. α - Methoxyimino - α - [2 - (chloroacetamido)thiazol - 4 - yl]acetic acid.

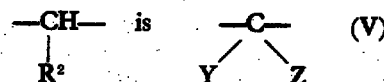
11. Ethyl α - methoxyimino - [2 - (β, β, β - trichloroethoxycarbonylamino)thiazol - 4 - yl]acetate.

12. A compound as claimed in claim 3, wherein R^5 represents a methoxy group.

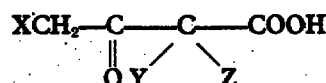
13. A compound as claimed in claim 3 wherein R^5 represents an ethoxy group.

14. A process for preparing a compound of the formula (I) as defined in claim 1, which comprises

(1) in the case where R^1 is an amino or hydroxyl group which may be protected and



where Y and Z are defined below, reacting a compound of the formula:

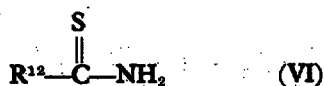




wherein X represents a halogen atom, Y represents hydrogen and Z represents an amino group which may be protected, or Y and Z together represent a group of the formula:

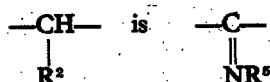


wherein R^5 represents a hydroxyl group which may be protected, or a salt or ester thereof, with a compound of the formula:

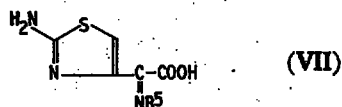


wherein R^{12} represents a C_1-C_4 alkoxy group or an amino group which may be protected, followed by, if necessary, removal of the protective group,

15 (2) where R^1 is hydroxyl and



reacting a compound of the formula:



20 wherein R^5 is as defined above, or a salt or ester thereof, with a diazotizing reagent, followed by, if necessary, removal of the protective group,

25 (3) where R_1 is amino or protected amino and R_2 is hydroxyl, reacting a compound of the formula:

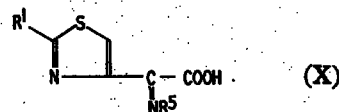


30 wherein R^{14} represents an amino group which may be protected, with a trihalogeno-acetone in the presence of a base to obtain a compound of the formula:



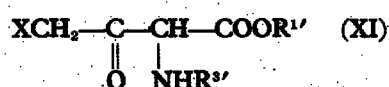
35 wherein R^{14} is as defined above, subjecting this compound to an addition reaction with hydrogen cyanide, acylating the cyanhydrin obtained and hydrolysing the resulting product, followed by, if necessary, removal of the protective group, or

40 (4) where R^1 is an amino or hydroxyl group which may be protected and R^2 is amino, reducing a compound of the formula:

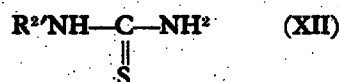


wherein R^1 and R^5 are as defined above, or a salt or ester thereof, followed by, if necessary, removal of the protective group.

15. A process for producing a 2 - aminothiazol - 4 - yl - glycine derivative of the general formula (IV) as defined in claim 7, which comprises reacting an α - amino - β - keto - γ - halogenobutyric acid ester of the general formula:

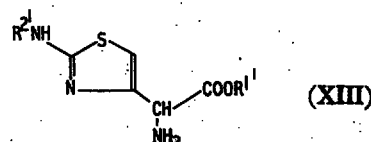


wherein X is a halogen atom, $-COOR^{1'}$ is a carboxyl group which may optionally be protected, and $R^{3'}NH-$ is an amino group which may optionally be protected, with a thiourea compound of the general formula:

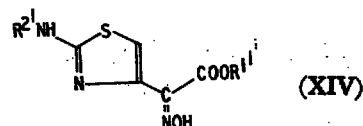


wherein R^2NH- is an amino group which may optionally be protected, and, if necessary, removing the protective group or groups.

16. A process for producing a 2 - aminothiazol - 4 - yl - glycine derivative of the general formula:

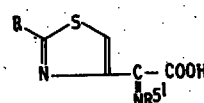


wherein $COOR^{1'}$ is an optionally protected carboxyl group and R^2NH is an optionally protected amino group, which comprises reducing a 2 - aminothiazole derivative of the general formula:



wherein R^2NH and $COOR^{1'}$ are as just defined, and, if necessary, removing the protective group or groups.

17. A process for preparing a compound of the formula:



wherein R represents a protected amino group and R^{51} represents a hydroxyl, methoxy or

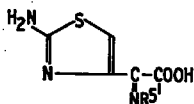


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ethoxy group, or a salt, an ester or a reactive derivative thereof, which comprises introducing a protective group onto a compound of the formula:



wherein the symbol R^5 has the same meaning as mentioned above, or a salt, an ester or a reactive derivative thereof.

10 18. A thiazole compound of the general formula (I) as defined in Claim 1, substantially as herein described with reference to any of the specific Examples.

15 19. A compound of the general formula (IV) as defined in Claim 7, substantially as herein described with reference to any of the specific Examples.

20. A process for preparing a compound of

formula (I) as defined in Claim 1, substantially as herein described with reference to any of the specific Examples.

21. A process for preparing a compound of formula (IV) as defined in Claim 7, substantially as herein described with reference to any of the specific Examples.

22. A compound of general formula (I) when prepared by a process claimed in any of claims 14 to 17, 20 and 21.

23. A compound of general formula (IV) when prepared by a process claimed in claim 15 or 21.

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