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NITROFURYL DERIVATIVES OF 5-SUBSTITUTED ISOXAZOLINES

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U.S. Cl. 260—307 F 7 Claims

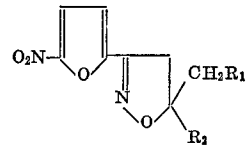
ABSTRACT OF THE DISCLOSURE

5-nitro-2-furyl-2-isoxazolines useful as antimicrobial agents; pharmaceutical compositions containing these compounds and methods for the treatment of microbial infections, particularly urinary tract infections and for the protection of organic material susceptible to microbial attack, employing these compounds. An illustrative embodiment is 5-cyanoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline.

DETAILED DISCLOSURE

The invention relates to nitrofuryl derivatives having valuable pharmacological properties and in particular to 5-nitro-2-furyl-2 - isoxazolines exhibiting antimicrobial activity. It further relates to pharmaceutical compositions containing these compounds as well as to methods for the treatment of mammals suffering from microbial infections, particularly urinary tract infections, by administering to said mammals an effective amount of a compound according to the invention. The invention also provides methods for protecting organic material susceptible to microbial attack by treating said material with an effective amount of a compound according to the invention.

5-nitro-2-furyl-2-isoxazolines of the Formula I



(I)

wherein

R_1 represents chlorine or bromine; cyano, amino, 2,3-epoxypropoxy, morpholino, piperidino or pyrrolidino; the grouping —SR_3, —OR_3, —O.CO.R_3, —CH_2.CO.R_3 or —N(R_3).R_3, wherein R_3 represents alkyl having from 1 to 3 carbon atoms; the grouping —NH.CO.R_4, wherein R_4 represents alkoxy having from 1 to 3 carbon atoms, cycloalkyl having from 5 to 7 carbon atoms in the carbocyclic ring, alkyl having from 1 to 6 carbon atoms or alkyl having from 1 to 6 carbon atoms substituted by one or two chlorine atoms, bromine atoms, alkoxy groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, or cyano groups; ureido or ureido N-substituted by one to three alkyl groups, which alkyl groups may be the same or different and may each have from 1 to 3 carbon atoms; or when R_2 represents hydrogen, hydrogen also; and

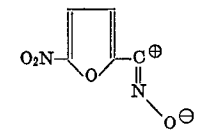
R_2 represents hydrogen or alkyl having from 1 to 3 carbon atoms have not been known up to now.

Of the compounds according to the invention, those wherein, in Formula I given above, R_1 represents chlorine or the grouping —NH.CO=R_4, wherein R_4 represents alkoxy having from 1 to 3 carbon atoms, cycloalkyl having from 5 to 7 carbon atoms in the carbocyclic ring, alkyl having from 1 to 6 carbon atoms or alkyl having

from 1 to 6 carbon atoms substituted by one or two chlorine atoms, bromine atoms, alkoxy groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, or cyano groups, and R_2 represents hydrogen or methyl, have been found to be of especial interest. Representative compounds of this scope which have been found to possess antimicrobial properties, especially antibacterial properties to a favourable degree are:

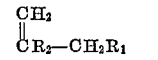
5-cyanoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline,
5-acetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline,
5-chloromethyl-5-methyl-3-(5-nitro-2-furyl)-2-isoxazoline,
5-methoxyacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline,
5-chloracetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, and
5-(3-methylureidomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline.

The subject 5-nitro-2-furyl-2-isoxazolines of the Formula I, given above may be prepared by reacting a 5-nitro-2-furyl nitrile oxide having the Formula II



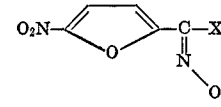
(II)

with an ethene derivative having the Formula III



(III)

The reaction is conveniently effected by generating the nitrile oxide of Formula II as required during the course of the reaction from the corresponding 5-nitro-2-furohydroxamoyl halide having the Formula IV



(IV)

wherein X represents halogen. The 5-nitro-2-furohydroxamoyl halide of Formula IV and the ethene derivative of Formula III are preferably contacted in the presence of a basic condensation promotor, for example sodium methoxide. If desired, the compound of Formula IV may be directly reacted with the compound of Formula III, preferably by heating together in the presence of toluene or other inert solvent.

The 5-nitro-2-furohydroxamoyl halide of Formula IV is preferably the chloride or bromide. The halides may be prepared by conventional methods: the chloride may be obtained, for instance, by the method described by Doyle, Hanson, Long and Nayler in the Journal of the Chemical Society (1963) at page 5845 or by that described in Helvetica Chimica Acta (1963) volume 46 at page 1067. The halide used as starting material in the process of the invention may be a purified product or it may be the crude product as prepared, if desired after partial purification.

The compounds of the invention have useful pharmacological and, in particular, antimicrobial properties, being valuable antibacterial, antifungal, antiviral, antihelminthic and coccidiostatic agents. The compounds are thus suitable for internal or external veterinary and medicinal use and are particularly valuable in the treatment of infections of the intestinal and, more especially, the urinary tract.

For example, in vivo and vitro tests indicate that the compound 5-cyanoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, a compound according to the present invention, exhibits antibacterial activity to a marked degree, e.g. in a test with experimental cystopyelitis in adult rats, involving administration of a total of five dosages of 50 mg./kg. each, P.O., over a two-day period, with sacrifice and examination of the rats on day three after initial infection. In vivo tests further indicate that after oral administration of a dosage as low as e.g. 200 mg./kg. to adult rats, antimicrobially effective amounts of the said 5-cyanoacetamidomethyl-3-(5 - nitro - 2 - furyl)-2-isoxazoline, are observable in the urine, indicating the effectiveness of the compound in the bladder and urinary tract. In addition to the foregoing, the sub-chronic toxicity of, e.g. 5-cyanoacetamido - 3 - (5-nitro-2-furyl)-2-isoxazoline and 5-chloracetamidomethyl - 3 - (5-nitro-2-furyl)-2-isoxazoline on oral administration to mice has been found to be of low order.

In accordance with the foregoing the present invention further provides a method for the treatment of a mammal suffering from a microbial infection, which method comprises administering to said mammal a therapeutically effective amount of a compound of the Formula I as hereinbefore defined, and in a particular aspect the invention provides a method for the treatment of a mammal suffering from a urinary tract, microbial infection, which method comprises administering to said mammal a therapeutically effective amount of a compound of the Formula I as hereinbefore defined. In both of the above methods the specific compounds listed above are of special interest.

The pharmaceutical compositions according to the invention contain at least one compound of General Formula I as active substance together with a conventional pharmaceutical carrier. The type of carrier actually used depends to a great extent on the intended application: for external use, for example in disinfecting healthy skin, disinfecting wounds and in treating dermatoses and affections of the mucous membranes caused by bacteria, ointments, powders and tinctures are used in particular. The ointment bases may be anhydrous, for instance, they can consist of mixtures of wool fat and soft paraffin, or they can consist of aqueous emulsions in which the active substance is suspended. Suitable carriers for powders are, for instance, rice starch and other starches; the bulk weight of the carriers may be made lighter, if desired, for example by adding highly dispersed silicic acid, or may be made heavier by adding talcum. The tinctures may contain at least one active ingredient of the Formula I in aqueous ethanol, in particular 45% to 75% by weight ethanol, to which 10% to 20% by weight of glycerol may be added, if desired. Solutions prepared from polyethylene glycol and other conventional solubility promoters, and also optionally, from emulsifying agents, may be used with particular advantage in disinfecting healthy skin. The content of active ingredient in pharmaceutical compositions for external application is preferably in the range of from 0.1% to 5% by weight.

Gargles or concentrates for their preparation, and tablets for slow dissolution in the mouth, are suitable for the disinfection of the mouth and throat. The former are preferably prepared from alcoholic solutions containing 1% to 5% by weight of active substance to which glycerol or flavourings may be added. Lozenges, that is solid dosage units, preferably have a relatively high content of sugar or similar substances and a relatively low content of active substance, for instance 0.2% to 20% by weight, as well as the usual conventional additives such as binding agents and flavourings.

Solid dosage units, in particular tablets, dragées (sugar coated tablets) and capsules, are convenient for use in intestinal disinfection and for the oral treatment of urinary tract infections. These units preferably contain from 10% to 90% by weight of the compound of the general Formula I to enable the administration of daily doses of from 0.1 to 2.5 grams to adult mammals, or of suitably reduced doses to children, to be made. Tablets and dragée cores are produced by combining the compounds of the general Formula I with solid, pulverulent carriers such as lactose, saccharose, sorbitol, maize starch, potato starch or amylopectin, cellulose derivatives or gelatines, preferably with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols of suitable molecular weight. Dragée cores may then be coated, for example with concentrated sugar solutions which can also contain gum arabic, talcum and/or titanium dioxide, or they may be coated with a lacquer dissolved in volatile organic solvents or mixture of solvents. Dyestuffs can be added to these coatings, for instance to differentiate between varying dosages. Soft gelatine capsules and other closed capsules consist, for example, of a mixture of gelatines and glycerol and may contain, for example mixtures of a compound of Formula I with polyethylene glycol. Hard gelatine capsules contain, for example, granulates of an active substance with solid pulverulent carriers, for instance lactose, saccharose, sorbitol, mannitol, starches (such as potato starch, maize starch or amylopectin), cellulose derivatives of gelatine, and magnesium stearate or stearic acid.

In all forms for administration, compounds of the General Formula I can be present as sole active ingredients or they can also be combined with other known pharmacologically active, and especially antibacterial and/or antimycotically or other antimicrobially active substances, for example, to broaden the range of application. They can be combined for example, with 5,7-dichloro-2-methyl-8-quinolinol or other derivatives of 8-quinolinol, with sulfamerazine or sulfafurazole or other derivatives of sulfanilamide, with chloroamphenicol or tetracycline or other antibiotica, with 3,4',5-tribromosalicylamide or other halogenated salicylanilides, with halogenated carbanilides, with halogenated benzoxazoles or benzoxazolones, with polychlorohydroxy-diphenylmethanes, with halogen-dihydroxydipheyl sulphides, with 4,4'-dichloro-2-hydroxy-diphenylether or 2',4,4'-trichloro-2-hydroxydiphenylether or other polyhalogen-hydroxydiphenylethers, or with bactericidal quaternary compounds or with certain dithiocarbamic acid derivatives such as tetramethylthiuram disulphide. Also, carriers which themselves have favourable pharmacological properties may be used, for instance sulphur as a powder base or zinc stearate as a component of ointment bases.

Daily dosages, for example for the treatment of urinary tract infections, are preferably of the order of from about 1 to 100, or more preferably from about 1 to 40 mg./kg. administered orally.

As noted above the compounds of the invention have been shown to exhibit valuable antimicrobial and notably anti-bacterial properties in vitro and are thus suitable for use in the protection of organic materials susceptible to microbial attack. Such organic material include synthetic polymeric materails, proteinaceous or carbohydrate substances or natural or synthetic fibres or textile materials produced therefrom.

In accordance with the foregoing the present invention further provides a method for protecting organic material susceptible to microbial attack, which process comprises treating said material with an effective amount of a compound of the Formula I as hereinbefore defined. Again the specific compounds listed above are of especial interest in this connection.

The following examples illustrate the present invention, but are in no way intended to limit it. Throughout the present Specification and the following examples, temperatures are given in degrees centigrade, and all percentages are given by weight.

EXAMPLE 1

A solution of 2.3 grams of metallic sodium dissolved in 50 millilitres of anhydrous methanol was added slowly to

a mixture of 19.1 grams of 5-nitro-2-furohydroxamoyl chloride and 6.7 grams of allyl cyanide dissolved in 150 millilitres of anhydrous methanol at 10° to 15°. After allowing to stand, the crystalline precipitate which formed was collected, washed with water and recrystallised from a mixture of water and ethanol.

The product was 5-cyanomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 165°.

EXAMPLE 2

The procedure described in Example 1 was carried out using the molecular equivalent of allyl methyl sulphide as starting material instead allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-methylmercaptomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 130°.

EXAMPLE 3

The procedure described in Example 1 was carried out using the molecular equivalent of allyl glycidyl ether as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(2,3-epoxy-1-propoxymethyl)-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 81°.

EXAMPLE 4

The procedure described in Example 1 was carried out using the molecular equivalent of allyl acetate as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-acetoxymethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 136°.

EXAMPLE 5

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylacetamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5 - acetamidomethyl - 3 - (5-nitro-2-furyl)-2-isoxazoline, having melting point 164°.

EXAMPLE 6

The procedure described in Example 1 was carried out using the molecular equivalent of allylacetone as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(but-3-one-1-yl)-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 110°.

EXAMPLE 7

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylcyanoacetamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-cyanoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 156°.

EXAMPLE 8

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylurea as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 3 - (5 - nitro - 2 - furyl) - 5 - ureidomethyl-2-isoxazoline, having melting point 218° with decomposition.

EXAMPLE 9

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylurethane as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(N-ethoxycarbonylaminomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 118°.

EXAMPLE 10

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylmorpholine as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-morpholinomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 130°.

EXAMPLE 11

The procedure described in Example 1 was carried out using the molecular equivalent of allyl bromide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-bromomethyl-3-(5-nitro-2-furyl)-2-isoxazoline having melting point 105°.

EXAMPLE 12

The procedure described in Example 1 was carried out using the molecular equivalent of methallyl chloride as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-chloromethyl-5-methyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 113°.

EXAMPLE 13

A solution of 2.3 grams of metallic sodium dissolved in 50 millilitres of anhydrous methanol was added slowly to a solution of 19.1 grams of 5-nitro-2-furohydroxamoyl chloride dissolved in 150 millilitres of anhydrous methanol through which was passed a continuous stream of propylene gas and which was maintained at 10° to 15°. After allowing to stand the crystalline precipitate which formed was collected, washed with water and recrystallised from a mixture of water and ethanol.

The product was 5-methyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 137°.

EXAMPLE 14

The procedure described in Example 1 was carried out using the molecular equivalent of allylamine as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-aminomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 187° with decomposition.

EXAMPLE 15

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylpiperidine as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 3-(5-nitro-2-furyl)-5-piperidinomethyl-2-isoxazoline.

EXAMPLE 16

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylpyrrolidine as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 3-(5-nitro-2-furyl)-5-pyrrolidin-1-ylmethyl-2-isoxazoline.

EXAMPLE 17

The procedure described in Example 1 was carried out using the molecular equivalent of N,N-diethylallylamine as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(N,N-diethylaminomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline. Similarly by using the molecular equivalent of any of the following reactants instead of N,N-diethylallylamine, N,N-dimethylallylamine, N,N-di-propylallylamine, the following products are obtained, respectively: 5-(N,N - dimethylaminomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline, 5 - (N,N-di-n-propylaminomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline.

EXAMPLE 18

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylisobutyramide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(isobutyramidomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 161°.

EXAMPLE 19

The procedure described in Example 1 was carried out using the molecular equivalent of N-allylhexanamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(hexanamidomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline.

EXAMPLE 20

The procedure described in Example 1 was carried out using the molecular equivalent of N-allyl-chloroacetamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-chloroacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 148°.

EXAMPLE 21

The procedure described in Example 1 was carried out using the molecular equivalent of N-allyl-dichloroacetamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-dichloroacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 187°.

EXAMPLE 22

The procedure described in Example 1 was carried out using the molecular equivalent of N-allyl-bromoacetamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-bromoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline.

EXAMPLE 23

The procedure described in Example 1 was carried out using the molecular equivalent of N-allyl-methoxyacetamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-methoxyacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 144°.

EXAMPLE 24

A solution of 10 grams of 5-cyanoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline dissolved in 200 millilitres of anhydrous ethanol was saturated with anhydrous hydrogen chloride gas at 20° to 30°. After allowing to stand, 100 millilitres of water was added and the mixture was heated to 60° and then cooled. The crystalline precipitate which formed was collected, washed with water and recrystallised from a mixture of water and ethanol.

The product was 5-(ethoxycarbonyl-acetamidomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline.

EXAMPLE 25

The procedure described in Example 1 was carried out using the molecular equivalent of N-allyl-cyclohexanecarboxamide as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(N-cyclohexanecarbox-amidomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 158°.

EXAMPLE 26

The procedure described in Example 1 was carried out using the molecular equivalent of 1-allyl-3-methylurea as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-(3-methylureidomethyl)-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 216°.

EXAMPLE 27

The procedure described in Example 1 was carried out using the molecular equivalent of allyl-isopropyl ether as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-isopropoxymethyl-3-(5-nitro-2-furyl)-2-isoxazoline, having melting point 79°.

EXAMPLE 28

The procedure described in Example 1 was carried out using the molecular equivalent of allyl-chloride as starting material instead of allyl cyanide, the reaction conditions being otherwise essentially the same.

The product was 5-chloromethyl-3-(5-nitro-2-furyl)-2-isoxazoline having melting point 102°.

EXAMPLE 29

Preparation of tablets

100 g. of active substance, e.g., of 5-cyanoacetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline are mixed with 60.0 g. of maize starch and 35.0 g. of lactose, the mixture is moistened with a solution of 5.0 g. of gelatin and 3.0 g. of glycerol in 70.0 g. of water and granulated through a sieve. The granulate is mixed with a mixture of 15.0 g. of talcum, 10.0 g. of maize starch and 2.0 g. of magnesium stearate. The resulting mixture is pressed into 1,000 tablets each containing 100 mg. of active substance. If desired the tablets can be grooved for better adaptation of the dosage.

EXAMPLE 30

PREPARATION OF DRAGEES

Composition:	For 1,000 dragees (g.)
(I)	
Active substance, e.g. 5-chloracetamidomethyl-3-(5-nitro-2-furyl)-2-isoxazoline	100.0
Maize starch	27.0
Gelatin	8.0
(II)	
Glycerol	2.0
Distilled water q.s. ad 100 ml.	
Maize starch	10.0
(III)	
Talcum	7.0
Magnesium stearate	1.0
	155.0
(IV)	
White dragee coating	
Shellac	2.0
Sugar	50.0
Talcum	38.0
Gum arabic	7.4
Colloidal silicon dioxide	2.2
Titanium dioxide	0.4

Composition I is granulated in the heat with composition (II) through a sieve of 1.2 mm. mesh diameter. The dried granulate is mixed with composition (III) and the resulting mixture is pressed into 1,000 dragee cores. These are then coated with composition (IV) and dried. The dragees obtained weigh 255.0 mg. and contain 100 mg. of active substance.

EXAMPLE 31

PREPARATION OF A SYRUP

Composition:	For 1 litre (g.)
Active substance, e.g. 5-methoxyacetamido-methyl-3-(5-nitro-2-furyl)-2-isoxazoline	100.0
Colloidal silicon dioxide	13.0
p-Hydroxybenzoic acid methyl ester	1.4
p-Hydroxybenzoic acid propyl ester	0.6
Citric acid	1.0
Sodium cyclamate	5.0
Distilled water	610.0
Glycerol	100.0
Sodium carboxymethyl cellulose	4.0
Sugar	320.0
	1155.0

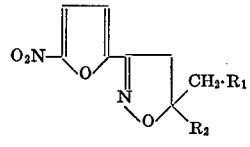
The active substance and the colloidal silicon dioxide are passed through a sieve of 1.2 mm. mesh diameter (I).

The p-hydroxybenzoic acid esters, the citric acid and the sodium cyclamate are dissolved in the given amount of boiling distilled water; the glycerol is then added to this solution (II). The sodium carboxymethyl cellulose and the sugar are thoroughly mixed (III).

Composition (III) is then added at 75° C. to Solution (II) under stirring until complete dissolution of (III). The viscous, slightly turbid liquid is cooled to room temperature, filtered, if necessary, and mixed with composition (I). Water is added to the resulting mixture up to the prescribed weight of 1,155.0 g. and the syrup obtained is homogenised.

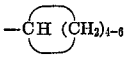
What we claim is:

1. A compound of the formula



wherein

R_1 represents the grouping —NH.CO.R_4, wherein R_4 represents alkoxy having from 1 to 3 carbon atoms, the group



alkyl having from 1 to 6 carbon atoms or alkyl having from 1 to 6 carbon atoms substituted by 1 or 2 chlorine atoms, bromine atoms, alkoxy groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, or cyano groups, ureido or ureido N-substituted by one to three alkyl groups, which alkyl groups may be the same or different and may each have from 1 to 3 carbon atoms; and

R_2 represents hydrogen or methyl.

2. A compound as defined in claim **1** wherein R_1 represents cyanoacetamido and R_2 represents hydrogen.

3. A compound as defined in claim **1** wherein R_1 represents acetamido and R_2 represents hydrogen.

4. A compound as defined in claim **1** wherein R_1 represents methoxyacetamido and R_2 represent hydrogen.

5. A compound as defined in claim **1** wherein R_1 represents chloroacetamido and R_2 represents hydrogen.

6. A compound as defined in claim **1** wherein R_1 represents methylureido and R_2 represents hydrogen.

7. A compound as claimed in claim **1**, wherein R_1 represents ureido and R_2 is hydrogen.

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ALTON D. ROLLINS, Primary Examiner

U.S. Cl. X.R.

260—247.5 R, 293.58, 346.1 R, 348 R; 424—272