PATENT SPECIFICATION

NO DRAWINGS

1,129,358

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Two Applications made in Japan (Nos. 55607 and 55608) on 10 Sept., 1965.
Complete Specification Published: 2 Oct., 1968.
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Index at acceptance:—C2 C(1J3C3, 2A1, 2A5, 2B2A4, 2B2G1B, 2B2G4, 2B2G5, 2B2J, 2B6A4, 2B6B, 2B6G4, 2B6G5, 2B6J, 2D19, 2R15, 3A8A4, 3A8B1, 3A8B2, 3A8C1, 3A8C7, 3A8G3, 3A8J, 3A8K, 3A19A4, 3A19B1, 3A19B2, 3A19C2, 3A19D1, 3C5A4, 3C5C2, 3C5C3, 3C5C7, 3C5E2, LZ32Y, LZ36Y, LZ214, LZ225, LZ250, LZ252, LZ305, LZ321, LZ322, LZ323, LZ351, LZ352, LZ360, LZ361, LZ366, LZ367, LZ368, LZ650, LZ660, LZ670, MF214, MF250, MF252, MF305, MF327, MF351, MF352, MF366, MF367, MF677, MF743)

Int. Cl.:—C 07 d 57/20

COMPLETE SPECIFICATION

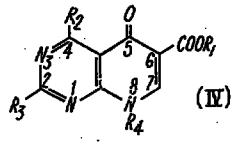
5,8-Dihydro-5-Oxopyrido[2,3-d]Pyrimidine Derivatives, and processes for the preparation thereof

We, DAINIPPON PHARMACEUTICAL CO. LTD., a Japanese body corporate of No. 25, 3-chome, Doshomachi, Higashi-ku, Osaka, Japan, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new compounds having anti-bacterial activity against Gram positive and Gram negative bacteria, and their production.

The compounds of this invention have a high activity against important pathogenic bacteria, especially Gram negative bacteria such as Shigella, Salmonella and Klebsiella. It can be expected that the compounds will be useful in treatment of bacterial infections in man and animals. Also, the compounds will be useful in the fields of foods and agriculture.

The new compounds of this invention are 5,8 - dihydro - 5 - oxopyrido[2,3-d]-pyrimidine derivatives represented by the following formula:



(IV)

wherein R_1 stands for hydrogen or a lower alkyl radical, R_2 stands for hydrogen, a lower alkyl radical, a hydroxy group, a halogen atom, a lower alkoxy radical, an amino group or a lower alkylthio radical, R_3 stands for hydrogen, a lower alkyl radical, a hydroxy group, a lower alkoxy radical, a lower alkylthio group or a radical of formula

$$-N<\begin{matrix}R'\\R''\end{matrix}$$

(in which R′ stands for hydrogen, an alkyl radical, a cycloalkyl radical, an amino group, a hydroxyalkyl radical or an alkyl-substituted aminoalkyl radical, R″ stands for hydrogen or an alkyl radical or R′ and R″, together with the nitrogen atom to which they are bonded, form a heterocyclic ring), and R_4 stands for hydrogen or an alkyl radical.

The term "lower alkyl radical" is used herein to mean a straight chain or branched chain alkyl radical having 1—6 carbon atoms, while "lower alkoxy radical" and "lower alkylthio radical" mean straight or branched chain alkoxy and alkylthio radicals having 1—6 carbon atoms.

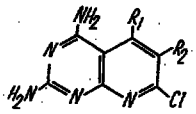
[*Price 4s. 6d.*]

The compounds of formula (IV) wherein R_4 is hydrogen may be considered as ketoenol tautomers with 5-hydroxy pyrido [2,3-d]pyrimidine derivatives. It will be understood that formula (IV) is to be regarded as including such an enol form.

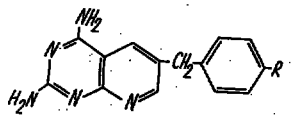
The compounds of formula (IV) wherein R_1 = hydrogen sometimes form organic amine salts, and such salts are within the scope of the invention. Examples are octadecylammonium and dodecylammonium salts.

Preferred compounds of formula (IV) are those in which R_2 is a hydrogen atom, a lower alkyl radical, a hydroxy group or a halogen atom. R_4 is preferably a lower alkyl radical.

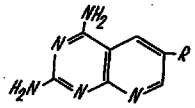
Certain compounds based on the same ring system, but having different substituents at the 5-position are known antibacterial agents. Typical examples are the compounds of the following formula, described in Belgian Patent Specification No. 658,069:



wherein R_1 stands for an alkyl radical having 1—4 carbon atoms, R_2 stands for hydrogen or an alkyl radical having 1—4 carbon atoms or an aralkyl radical, or R_1 and R_2 are alkylene groups which together with the carbon atoms of the ring to which they are attached, form an alicyclic ring, the compound of the following formula, described in Belgian Patent Specification No. 657,922:



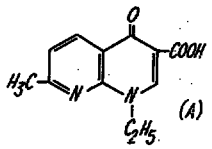
(wherein R stands for an alkoxy or alkyl radical having 1—4 carbon atoms), and the compounds of the following formula described in British Patent Specification No. 970,583:



(wherein R stands for an alkyl, phenalkyl or alkyl-substituted phenyl radical).

The compounds of formula (IV) are outstanding anti-bacterial agents in that they show a high anti-microorganism activity against many pathogenic microorganisms and their preparation is easy.

In Belgian Patent No. 612,258, a compound of different ring structure is described as an anti-bacterial agent having a high activity. This compound has the formula:



(A)

This compound has lower *in vitro* anti-bacterial activity and more toxicity than the preferred compounds of this invention. For instance, 6 - carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine [compound (B)] and 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido[2,3-d]pyrimidine, which are both compounds of this invention, show excellent anti-bacterial activities against a broad range of pathogenic microorganisms as will be shown later in Table III, and the MIC of said compound (B) is 10 mcg/ml against *staphylococcus aureus*, while that of the known compound (A) is 100 mcg/ml against the same organism.

In Table I below, the toxicity (LD_{50}) of the known compound (A) is compared with that of compound (B). It will be seen that the compound of the invention is far less toxic.

TABLE I

Acute toxicity in mice

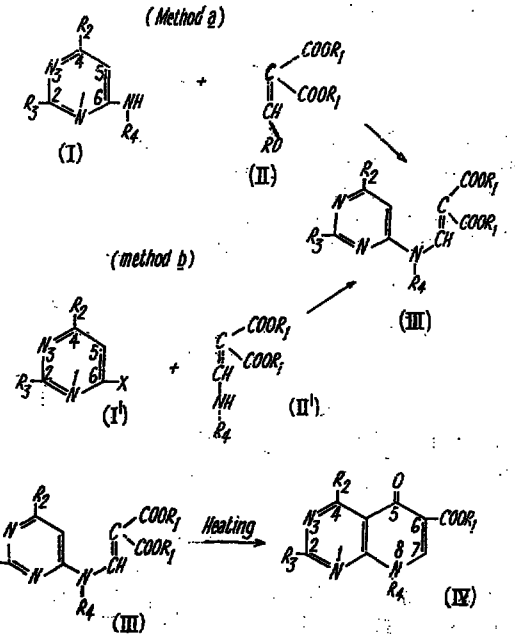
	dose	(survived/tested) i.p.	p.o.
compound (A)	1g/kg	0/5	3.5
compound (B)	lg/kg	4/5	5/5

Observation was made on 7th day after administration.

The following are preferred groups of compounds within formula (IV), from the view point of the broad scope of antibacterial applications and the excellent medicinal effect:

	R_1	R_3	R_4
(i)	hydrogen		alkyl
(ii)	hydrogen or lower alkyl	lower alkyl-thio or $-N<^{R'}_{R''}$	hydrogen or alkyl (preferably lower alkyl)

The novel compounds of this invention can be easily prepared by ring-closure upon heating intermediates of formula (III) (which are themselves novel compounds). An N-(6-pyrimidinyl) amino-methylenemalonic acid or ester of formula (III) can be prepared by two general methods. The whole general scheme is set out below:



(wherein R_1, R_2, R_3 and R_4 are as defined in formula (IV), R stands for a lower alkyl radical and X stands for a halogen atom).

As shown above, method *a* involves reaction of an aminopyrimidine derivative of formula (I) with an alkoxymethylenemalonic acid or ester of formula (II), while method *b* involves reaction of a halogenopyrimidine derivative of formula (I') with an aminomethylenemalonic derivative of formula (II'). In both cases the intermediate of formula (III) is heated to produce the compound of formula (IV).

Method *a* may be carried out by heating the compound of formula (I) with the compound of formula (II) *per se* or in an inert solvent such as an alcohol or dioxane. The reaction temperature is 80—150°C., preferably 100—130°C.

Method *b* may be carried out by heating the compound of formula (I') with the compound of formula (II') in a sealed tube. This reaction may also be carried out in the absence of a solvent; however, it is better to carry out the reaction in an inert solvent such as an alcohol or dioxane. The reaction temperature is preferably within the range 80° to 150°C.

Heating to convert the intermediate of formula (III) into the compound of formula (IV) may be carried out in the absence of a solvent; however, preferably it is carried out in the presence of an inert organic solvent. The reaction temperature can vary from a fairly low temperature to a high temperature; however, normally a temperature of 100—300°C., preferably about 250°C., is adopted. Examples of suitable inert organic solvents are ethylene glycol monoalkyl ether, diphenyl ether or a mineral oil. The solvent will preferably be one having a boiling point in the vicinity of the reaction temperature, as it is best to carry out the reaction under reflux.

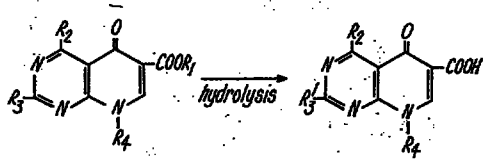
The reaction product may be purified by recrystallization according to any conventional method using, as occasion demands, a suitable solvent, which could well be methanol, ethanol, chloroform, butanol or acetone.

The compounds of formula (IV) may be inter-converted as explained below.

(1) Compounds of formula (IV) wherein R_1 is hydrogen, i.e. which have a free carboxylic acid group in the 6-position may be easily obtained by acid or alkaline hydrolysis of the corresponding esters (i.e. wherein R_1 is a lower alkyl radical). Usable hydrolysing agents include an alkali metal hydroxide or carbonate such as sodium hydroxide, potassium hydroxide or sodium carbonate, and mineral acids such as hydrochloric acid, sulphuric acid and phosphoric acid. When an alkaline hydrolysing agent is used, caustic alkalis (alkali metal hydroxides) are preferable to alkali metal carbonate. It is sufficient to heat the esters with the alkaline or acid hydrolysing agents for a short period. An excessively high temperature and/or an excessively long heating period is undesirable because of the tendency to bring about a side reaction. Generally, heating at a temperature below 100°C. for several minutes will do. When the 6-carboxylic ester is of formula (IV) wherein R_4 is an alkyl radical and R_3 is a lower alkoxy radical, or a lower alkylthio radical or a radical of formula

$$-N<^{R'}_{R''}$$

[R' and R'' being as hereinbefore defined], the R_3 substituent (at the 2-position) is hydrolyzed simultaneously with R_1 and converted to (or replaced by) a hydroxyl group. It is of course, also possible to hydrolyze a 6-carboxylic acid of formula (IV) wherein R_4 and R_3 have these meanings to produce the corresponding compound wherein R_3 is a hydroxy group. The hydrolysis reaction can be shown as follows:

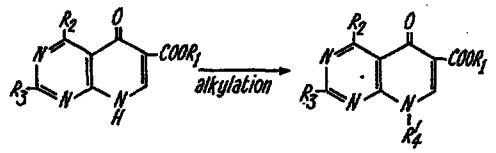


(wherein R'_3 stands for a hydroxy group when R_3 stands for a lower alkoxy group, a lower alkylthio group or

$$-N<^{R'}_{R''}$$

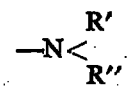
(wherein R' and R'' are as hereinbefore defined), and R_4 is an alkyl radical; otherwise R'_3 is the same as R_3, while R_1, R_2, R_3 and R_4 are as hereinbefore defined).

(2) Compounds of formula (IV) wherein R_4 is an alkyl radical, may be easily obtained from the corresponding compounds wherein R_4 is hydrogen by using alkylation processes. The reaction is shown below:

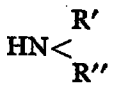


(wherein R_1, R_2 and R_3 are as hereinbefore defined and R'_4 stands for an alkyl radical). The alkylation may be carried out by using known alkylating agents, e.g. an alkyl halide, a dialkyl sulphate or an alkyl sulphonate. The reaction may be carried out by merely contacting the compound of formula (IV) wherein R_4 is hydrogen with these alkylating agents. For instance, when a dialkyl sulphate or an alkyl sulphonate is used, the reaction usually proceeds at room temperature merely by stirring. When an alkyl halide is used, normally it is better to carry out the reaction by heating, e.g. at about 100°C. Normally, the alkylation is best carried out in water or an organic solvent inert to the reaction system such as, for instance, N,N-dimethylformamide or an aliphatic alcohol in which the compound wherein R_4 is hydrogen can be dissolved or suspended. As mentioned above, the reaction may be carried out at room temperature or above. The alkylation may be accelerated by adding an alkaline catalyst, e.g. potassium carbonate, to the reaction system. However, in this case it will be understood that if the starting material is one in which R_1 is a lower alkyl radical, saponification of the 6-carboxylic ester is liable to occur, particularly if a caustic alkali, like sodium hydroxide or potassium hydroxide, is used.

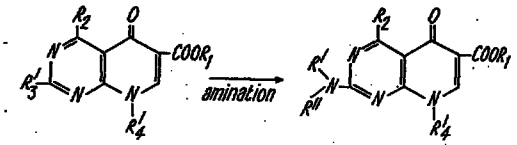
(3) Compounds of formula (IV) wherein R_3 is



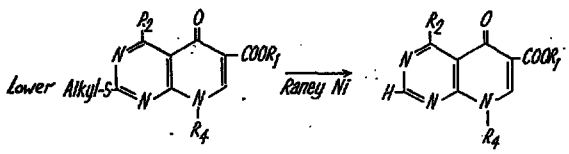
(R′ and R″ being as hereinbefore defined) can be obtained by reaction of amines of the formula



with compounds of formula (IV) wherein R_3 is a lower alkoxy or lower alkylthio radical. The reaction is illustrated below:



(wherein R_1, R_2, R′ and R″ are as hereinbefore defined, R'_3 stands for a lower alkoxy radical or a lower alkylthio radical, and R'_4 stands for an alkyl radical). This amination is normally carried out in a solvent inert to the reaction system under the reaction conditions e.g. water, an aliphatic alcohol, benzene, toluene, xylene, halogenoalkanes, tetrahydrofuran or dioxane. The reaction usually proceeds at room temperature, but it is better to use a temperature of 50°—150°C. It may be carried out under atmospheric or superatmospheric pressure; superatmospheric pressure, for instance 2—10 atmospheres, is preferred. Compounds of formula (IV) wherein R_3 is hydrogen are obtainable from those wherein R_3 is a lower alkylthio radical by desulphurization using Raney nickel. This reaction is illustrated below:



(wherein R_1, R_2 and R_4 are as hereinbefore defined). The reaction may be carried out in a suitable inert solvent such as an alcohol or dioxane at a temperature of 50°—200°C.

In Table II below compounds (1)—(9) are examples of intermediates of formula (III) which may be converted by heating into the compounds of the invention, and compounds Nos. (10)—(54) are examples of compounds of the invention.

TABLE II

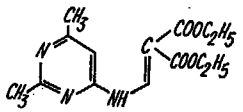
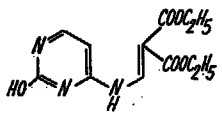
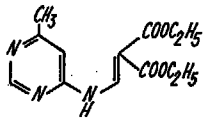
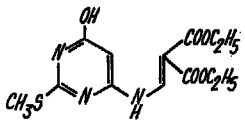
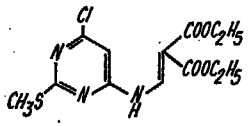
No.	Compound	Structure	m.p. °C.
1.	Ethyl N-(2,4-dimethyl-6-pyrimidinyl)-aminomethylenemalonate		102—103
2.	Ethyl N-(2-hydroxy-4-pyrimidinyl) aminomethylenemalonate		191—194
3.	Ethyl N-(4-methyl-6-pyrimidinyl) aminomethylenemalonate		101.5—102
4.	Ethyl N-(4-hydroxy-2-methylthio-6-pyrimidinyl)aminoethylenemalonate		228—230
5.	Ethyl N-(4-chloro-2-methylthio-6-pyrimidinyl)aminomethylene-malonate		132—134

TABLE II—*cont.*

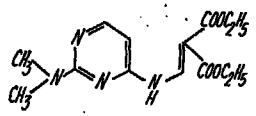
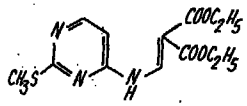
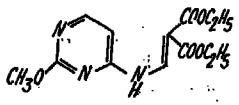
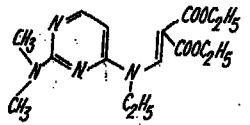
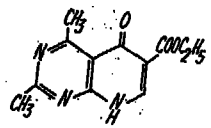
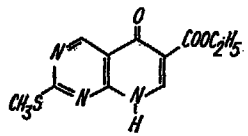
No.	Compound	Structure	m.p. °C.
6.	Ethyl N-(2-dimethylamino-4-pyrimidinyl) aminomethylenemalonate		64—65
7.	Ethyl N-(2-methylthio-4-pyrimidinyl) aminomethylenemalonate		106—107
8.	Ethyl N-(2-methoxy-4-pyrimidinyl) aminomethylenemalonate		123—125
9.	Ethyl N-(2-dimethylamino-4-pyrimidinyl)-N-ethyl aminomethylenemalonate		148—150
10.	5,8-Dihydro-2,4-dimethyl-6-ethoxycarbonyl-5-oxopyrido[2,3-d] pyrimidine		226—7
11.	5,8-Dihydro-6-ethoxycarbonyl-2-methyl-thio-5-oxopyrido[2,3-d] pyrimidine		269—271

TABLE II—*cont.*

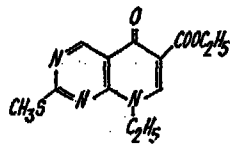
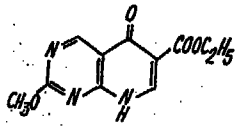
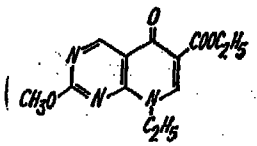
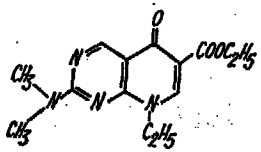
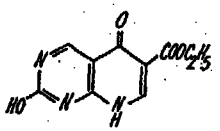
No.	Compound	Structure	m.p. °C.
12.	5,8-Dihydro-6-ethoxycarbonyl-8-ethyl-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		144.5—145.5
13.	5,8-Dihydro-6-ethoxycarbonyl-2-methoxy-5-oxopyrido[2,3-d] pyrimidine		235—7
14.	5,8-Dihydro-6-ethoxycarbonyl-8-ethyl-2-methoxy-5-oxopyrido[2,3-d]pyrimidine		147—9
15.	5,8-Dihydro-2-dimethylamino-6-ethoxy-carbonyl-8-ethyl-5-oxopyrido[2,3-d]-pyrimidine		163—164.5
16.	5,8-Dihydro-6-ethoxycarbonyl-2-hydroxy-5-oxopyrido[2,3-d] pyrimidine		258—261

TABLE II—*cont.*

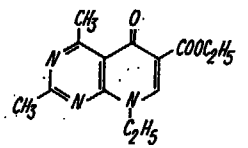
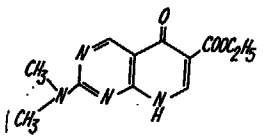
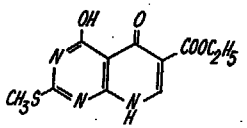
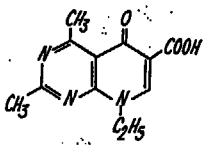
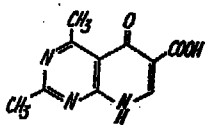
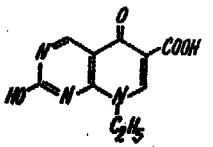
No.	Compound	Structure	m.p. °C.
17.	5,8-Dihydro-2,4-dimethyl-6-ethoxycarbonyl-8-ethyl-5-oxopyrido[2,3-d] pyrimidine		156.5—158
18.	5,8-Dihydro-2-dimethylamino-6-ethoxycarbonyl-5-oxopyrido[2,3-d] pyrimidine		290—295
19.	5,8-Dihydro-6-ethoxycarbonyl-4-hydroxy-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		261—263
20.	6-Carboxy-5,8-dihydro-2,4-dimethyl-8-ethyl-5-oxopyrido[2,3-d]pyrimidine		222—224
21.	6-Carboxy-5,8-dihydro-2,4-dimethyl-5-oxopyrido[2,3-d] pyrimidine		266—7
22.	6-Carboxy-5,8-dihydro-8-ethyl-2-hydroxy-5-oxopyrido[2,3-d]pyrimidine		287—292

TABLE II—*cont.*

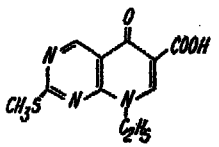
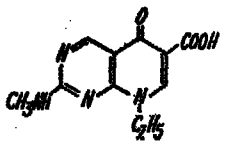
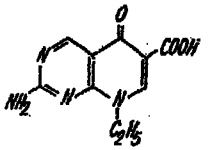
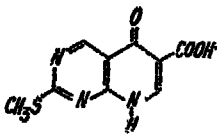
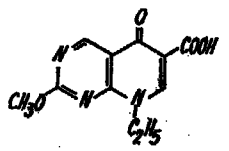
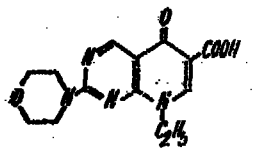
No.	Compound	Structure	m.p. °C.
23.	6-Carboxy-5,8-dihydro-8-ethyl-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		253—256
24.	6-Carboxy-5,8-dihydro-8-ethyl-2-methylamino-5-oxopyrido[2,3-d] pyrimidine		274—6
25.	2-Amino-6-carboxy-5,8-dihydro-8-ethyl-5-oxopyrido[2,3-d] pyrimidine		291—293
26.	6-Carboxy-5,8-dihydro-2-methylthio-5-oxopyrido[2,3-d] pyrimidine		279—281
27.	6-Carboxy-5,8-dihydro-8-ethyl-2-methoxy-5-oxopyrido[2,3-d]pyrimidine		254—6
28.	6-Carboxy-5,8-dihydro-8-ethyl-2-morpholino-5-oxopyrido[2,3-d]pyrimidine		270—272

TABLE II—*cont.*

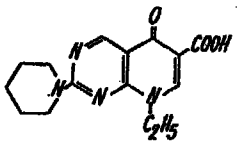
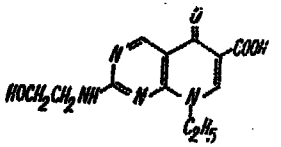
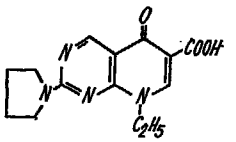
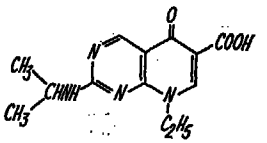
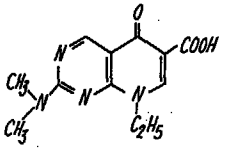
No.	Compound	Structure	m.p. °C.
29.	6-Carboxy-5,8-dihydro-8-ethyl-5-oxo-2-piperidino-pyrido[2,3-d]pyrimidine		267—270
30.	6-Carboxy-5,8-dihydro-8-ethyl-2-(2-hydroxyethyl)amino-5-oxopyrido[2,3-d]-pyrimidine		268—270
31.	6-Carboxy-5,8-dihydro-8-ethyl-5-oxo-2-pyrrolidino-pyrido[2,3-d]pyrimidine		314—6
32.	6-Carboxy-5,8-dihydro-8-ethyl-2-iso-propylamino-5-oxopyrido[2,3-d] pyrimidine		233—235
33.	6-Carboxy-5,8-dihydro-2-dimethylamino-8-ethyl-5-oxopyrido[2,3-d]pyrimidine		288—291

TABLE II—*cont.*

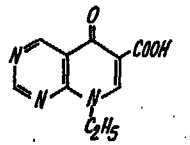
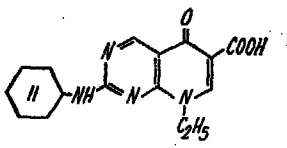
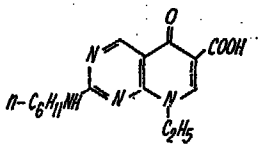
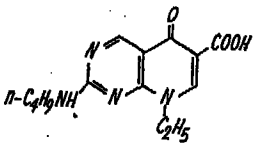
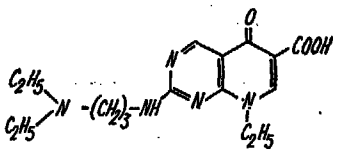
No.	Compound	Structure	m.p. °C.
34.	6-Carboxy-5,8-dihydro-8-ethyl-5-oxo-pyrido[2,3-d]pyrimidine		219—222
35.	6-Carboxy-2-cyclohexylamino-5,8-dihydro-8-ethyl-5-oxopyrido[2,3-d] pyrimidine		209—211
36.	6-Carboxy-5,8-dihydro-8-ethyl-2-n-hexylamino-5-oxopyrido[2,3-d]pyrimidine		164—6
37.	2-n-Butylamino-6-carboxy-5,8-dihydro-8-ethyl-5-oxopyrido[2,3-d] pyrimidine		192—194
38.	6-Carboxy-2-[3-(diethylamino)propylamino]-5,8-dihydro-8-ethyl-5-oxopyrido[2,3-d] pyrimidine		160—162

TABLE II—*cont.*

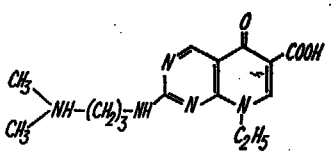
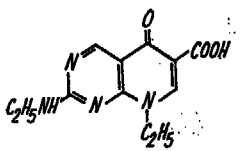
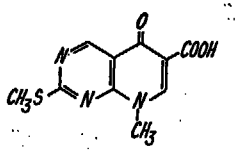
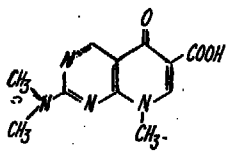
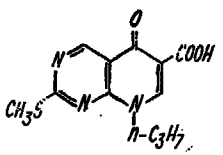
No.	Compound	Structure	m.p. °C.
39.	6-Carboxy-5,8-dihydro-2-[3-(dimethyl-amino)propylamino]-8-ethyl-5-oxopyrido-[2,3-d]pyrimidine		165—7
40.	6-Carboxy-5,8-dihydro-8-ethyl-2-ethyl-amino-5-oxopyrido[2,3-d]pyrimidine		269—272
41.	6-Carboxy-5,8-dihydro-8-methyl-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		299—302
42.	6-Carboxy-5,8-dihydro-2-dimethyl-amino-8-methyl-5-oxopyrido[2,3-d] pyrimidine		312—315
43.	6-Carboxy-5,8-dihydro-2-methylthio-5-oxo-8-n-propyl-pyrido[2,3-d]pyrimidine		197—9

TABLE II—*cont.*

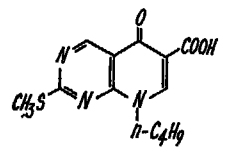
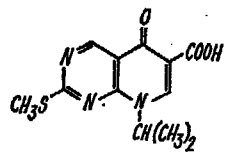
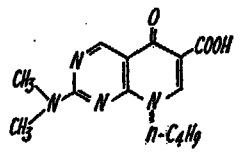
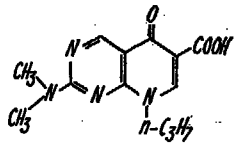
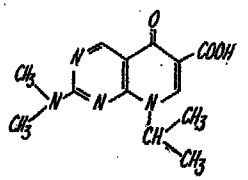
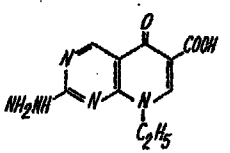
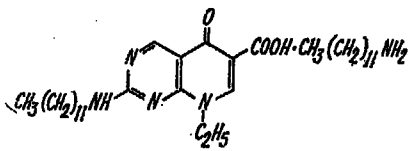
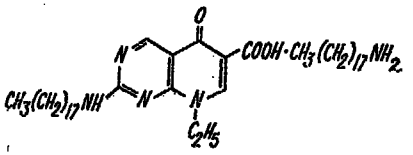
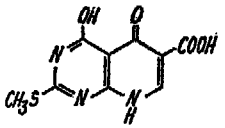
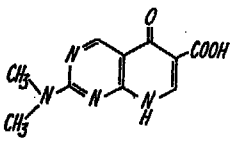
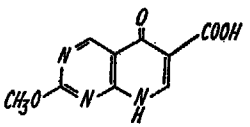
No.	Compound	Structure	m.p. °C.
44.	8-n-butyl-6-carboxy-5,8-dihydro-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		174—6
45.	6-Carboxy-5,8-dihydro-8-isopropyl-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		231—233
46.	8-n-Butyl-6-carboxy-5,8-dihydro-2-dimethylamino-5-oxopyrido[2,3-d] pyrimidine		205—7
47.	6-Carboxy-5,8-dihydro-2-dimethyl-amino-5-oxo-8-n-propyl-pyrido[2,3-d]-pyrimidine		261—262
48.	6-Carboxy-5,8-dihydro-2-dimethyl-amino-8-isopropyl-5-oxopyrido[2,3-d]-pyrimidine		251—253

TABLE II—*cont.*

No.	Compound	Structure	m.p. °C.
49.	6-Carboxy-5,8-dihydro-8-ethyl-2-hydrazino-5-oxopyrido[2,3-d]pyrimidine		259—261
50.	6-Carboxy-5,8-dihydro-2-dodecylamino-8-ethyl-5-oxopyrido[2,3-d]pyrimidine dodecylamine salt		160—163
51.	6-Carboxy-5,8-dihydro-8-ethyl-2-octadecylamino-5-oxopyrido[2,3-d]pyrimidine octadecylamine salt		160—163
52.	6-Carboxy-5,8-dihydro-4-hydroxy-2-methylthio-5-oxopyrido[2,3-d]pyrimidine		287—9
53.	6-Carboxy-5,8-dihydro-2-dimethylamino-5-oxopyrido[2,3-d]pyrimidine		300—305
54.	6-Carboxy-5,8-dihydro-2-methoxy-5-oxopyrido[2,3-d]pyrimidine		>250

The 5,8 - dihydro - 5 - oxopyrido[2,3-d]pyrimidine derivatives of this invention have antibacterial activity against Gram positive and Gram negative bacteria and tubercle bacilli, and are useful as intermediates for the preparation of other compounds having antibacterial activity.

The following Table III summarizes the in vitro antibacterial activities of the compounds against a variety of microorganisms. The minimum inhibitory concentration (MIC) was determined by well known serial dilution technique.

TABLE III

Antibacterial activity in Vitro

(MIC: mct/ml)

Organism \ Compound No.	(23)	(33)	(47)	(24)	(27)	(28)	(29)	(31)	(40)	(42)	(43)	(48)	(50)
Staphylococcus aureus	30	10	30	30	30	30	30	10	30	30	30	30	1
Escherichia coli	3	1	3	10	10	3	10	1	10	10	10	10	30
Shigella flexneri 2a	3	3	10	30	30	10	30	10	10	30	10	10	30
Shigella sonnei	1	1	3	10	10	3	10	3	10	10	10	10	30
Salmonella typhimurium	3	1	3	10	30	10	10	3	10	10	10	3	10
Proteus vulgaris	3	1	3	10	10	3	10	1	3	10	10	10	10
Klebsiella pneumoniae	1	0.3	1	3	3	1	3	1	1	3	3	3	3
Salmonella enteritidis	1	1	3	10	10	3	10	3	30	10	3	10	30
Mycobacterium tuberculosis	30	10	30	10	30	10	30	—	30	30	10	30	30

The table IV summarizes in vivo activities of the compound against infection with Salmonella typhimurium in mice.

TABLE IV

Therapeutic effect in mice

Organism: Salmonella typhimurium
Route of Infection: i.p.
Route of Administration: p.o.
(survived/tested)

compound No.	(12)	(15)	(23)	(33)
route / dose*	p.o.	p.o.	p.o.	p.o.
100 mg/kg	6/10	8/10	6/20	6/10
50 „	4/10	7/10	2/10	5/10
25 „	1/10	5/10	—	4/10
12.5 „	—	3/10	—	3/10

Survival rate of non-treated control was 0/10.

* 2 times per day for 4 days.

The compounds of this invention may be used in external, oral and injectable forms or in combination with other drugs.

The following Examples illustrate the invention.

EXAMPLE 1

(Example of synthesis of a compound of formula (III) according to method *a*).

6-Amino-2,4-dimethylpyrimidine (12.2 g) and 23.0 g of ethyl ethoxymethylenemalonate were heated, while stirring, for 35 minutes at a temperature of 110 to 120°C. The resulting product was cooled and recrystallised from ethanol. There were obtained 18.5 g of ethyl N - (2,4 - dimethyl - 6 - pyrimidinyl) aminomethylenemalonate having a melting point of 102 to 103°C.

EXAMPLE 2

(Example of synthesis of a compound of formula (III) according to method *a*).

6 - Amino - 2 - methylthiopyrimidine (29.0 g) and 60.0 g of ethyl ethoxymethylenemalonate were heated, while stirring, for 1 hour and 40 minutes at a temperature of 135 to 140°C. The resulting product was cooled and recrystallised from ethanol. There were obtained 33.7 g of ethyl N - (2 - methylthio - 6 - pyrimidinyl)aminomethylenemalonate having a melting point of 106 to 107°C.

EXAMPLE 3

(Example of synthesis of a compound of formula (III) according to method *a*).

6-Amino-2-methoxypyrimidine (2.06 g) and 4.20 g of ethyl ethoxymethylenemalonate were heated, while stirring, for 1 hour and 10 minutes at a temperature of 135 to 140°C. The resulting product was cooled and recrystallised from ethanol. There were obtained 2.66 g of ethyl N - (2 - methoxy - 6 - pyrimidinyl) aminomethylenemalonate having a melting point of 123 to 125°C.

EXAMPLE 4

(Example of synthesis of a compound of formula (III) according to method *a*).

6-Amino-2-hydroxypyrimidine (1.4 g) and 3.0 g of ethyl ethoxymethylenemalonate were subject to reaction for 20 minutes at 150 to 160°C. After cooling the reaction product, the obtained crystals were recrystallised from ethanol. There were obtained 2.4 g of ethyl N - (2 - hydroxy - 6 - pyrimidinyl)aminomethylenemalonate having a melting point of 191—194°C.

The following compounds were obtained by the same method as above mentioned.
(1) Ethyl N-(4-methyl-6-pyrimidinyl) aminomethylenemalonate having a melting point of 101.5—102°C. from 6-amino-4-methylpyrimidine and ethyl ethoxymethylenemalonate.
(2) Ethyl N-(4-hydroxy-2-methylthio-6-pyrimidinyl) aminomethylenemalonate having a melting point of 228—230°C. from 6-amino-4-hydroxy-2-methylthiopyrimidine and ethyl ethoxymethylenemalonate.
(3) Ethyl N-(4-chloro-2-methylthio-6-pyrimidinyl) aminomethylenemalonate having a melting point of 132—134°C. from 6-amino-4-chloro-2-methylthio-pyrimidine and ethyl ethoxymethylenemalonate.
(4) Ethyl-N-(2-dimethylamino-6-pyrimidinyl) aminomethylenemalonate having a melting point of 59—63°C. from 6-amino-2-dimethylaminopyrimidine and ethyl ethoxymethylenemalonate.

EXAMPLE 5

(Example of synthesis of a compound of formula (III) according to method *a*).

A mixture of 1.0 g of 2-dimethylamino-6-ethylaminopyrimidine and 1.4 g of ethyl ethoxymethylenemalonate was stirred for 2 hours at 145°C. and then distilled under reduced pressure. There was obtained 760 mg of ethyl N - (2 - dimethylamino - 6 - pyrimidinyl) - N - ethylaminomethylenemalonate. The picrate of this compound has a melting point of 148—150°C.

EXAMPLE 6

(Example of synthesis of a compound of formula (III) according to method *b*).

6-Chloro-2-dimethylaminopyrimidine (200 mg) and 300 mg of ethyl aminomethylenemalonate were added to 30 ml of ethanol, and the mixture was reacted for 6 hours at 140°C. in a sealed tube. At the end of the reaction, the solvent was removed by distillation under reduced pressure. The resulting product was recrystallised from ethanol to give 280 mg of ethyl N-(2-dimethylamino-6-pyrimidinyl) aminomethylenemalonate having a melting point of 59—63°C.

The following compounds were obtained in the same manner as above mentioned.
(1) Ethyl N-(2-methylthio-6-pyrimidinyl) aminomethylenemalonate having a melting point of 106—107°C. from 6-chloro-2-methylthiopyrimidine and ethyl aminomethylenemalonate.
(2) Ethyl N-(2-methoxy-6-pyrimidinyl)aminomethylenemalonate having a melting point of 123—125°C. from 6-chloro-2-methoxypyrimidine and ethyl aminomethylenemalonate.

EXAMPLE 7

(Example of synthesis of a compound of the formula (IV) from a compound of formula (III)).

Ethyl N-(2,4-dimethyl-6-pyrimidinyl) aminomethylenemalonate obtained in Example 1 (4.20 g) was added to 60 g of boiling diphenyl ether, and the mixture was vigorously heated under reflux for 15 minutes. After cooling, 300 ml of n-hexane was added to the product. The precipitated crystals were recovered by filtration and recrystallised from ethanol to give 2.30 g of 5,8 - dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 5 - oxopyrido [2,3-d]pyrimidine having a melting point of 266—267°C.

EXAMPLE 8

(Example of synthesis of a compound of formula (IV) from a compound of formula (III)).

Ethyl N-(2-methylthio-6-pyrimidinyl) aminomethylenemalonate obtained in Example 2 (43.0 g) was added to 270 ml of boiling diphenyl ether, and the mixture was heated under reflux for 25 minutes. After cooling, 400 ml of n-hexane was added to the product. The precipitated crystals were recovered by filtration and washed with ethanol to give 26.4 g of 5,8-dihydro-6-ethoxycarbonyl-2-methylthio-5-oxopyrido [2,3-d] pyrimidine having a melting point of 269—271°C.

EXAMPLE 9

(Example of synthesis of a compound of formula (IV) from a compound of formula (III)).

Ethyl N-(2-methoxy-6-pyrimidinyl) aminomethylenemalonate obtained in Example 3 (1.16 g) was added to 15 ml of boiling diphenyl ether, and the mixture was vigorously heated under reflux for 10 minutes. After cooling, 50 ml of n-hexane was added to the product. The precipitated crystals were recovered by filtration and recrystallised from ethanol to give 0.64 g of 5,8-dihydro-6-ethoxycarbonyl-2-methoxy-5-oxopyrido [2,3-d]pyrimidine having a melting point of 235—237°C.

EXAMPLE 10

(Example of synthesis of a compound of formula (IV) from a compound of formula (III)).

Ethyl N-(2-hydroxy-6-pyrimidinyl) aminomethylenemalonate (610 mg) was added to 5 ml of boiling diphenyl ether, and the mixture was heated for 10 minutes under reflux. After cooling, 10 ml of n-hexane was added to the product. The precipitated crystals were recovered by filtration, and recrystallised from methanol to give 330 mg of 5,8 - dihydro - 6 - ethoxycarbonyl - 2 - hydroxy - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 258—261°C.

EXAMPLE 11

(Example of synthesis of a compound of formula (IV) from a compound of formula (III)).

Ethyl N-(4-hydroxy-2-methylthio-6-pyrimidinyl) aminomethylenemalonate (2.10 mg) was added to 3 ml of diphenyl ether, and the mixture was refluxed for 13 minutes. To the product was added 15 ml of n-hexane. The precipitated crystals were recovered by filtration and recrystallised from ethanol-chloroform to give 20 mg of 5,8-dihydro-6-ethoxycarbonyl-4-hydroxy-2-methylthio-5-oxopyrido [2,3-d] pyrimidine having a melting point of 261—263°C.

EXAMPLE 12

(Example of synthesis of a compound of formula (IV) from a compound of formula (III)).

Ethyl N-(2-dimethylamino-6-pyrimidinyl) aminomethylenemalonate (10 g) was added to 50 ml of diphenyl ether under reflux, and the mixture was reacted for 20 minutes. After cooling, 200 ml of n-hexane was added to the product. The precipitated crystals were recovered by filtration, and washed with ethanol to give 8.0 g. of 5,8 - dihydro - 2 - dimethylamino - 6 - ethoxycarbonyl - 5 - oxopyrido [2,3-d]pyrimidine having a melting point of 290—295°C.

EXAMPLE 13

(Example of conversion of a compound of formula (IV) by alkylation into another compound of formula (IV)).

A mixture of 2.9 g of 5,8 - dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 5 - oxopyrido [2,3-d] pyrimidine, 25 g of N,N-dimethylformamide, 10 g of ethyl iodide and 10 ml of a 20% aqueous solution of potassium carbonate were stirred for 1 hour at 100°C. The precipitated potassium iodide was separated by filtration, and dimethylformamide was removed by distillation under reduced pressure. A saturated aqueous sodium chloride solution was added to the resulting product, and it was extracted with chloroform, followed by recrystallisation from ethanol. There was obtained 1.95 g of 5,8 - dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 8 -ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 156.5—158°C.

EXAMPLE 14

(Example of conversion of a compound of formula (IV) by alkylation into another compound of formula (IV)).

A mixture of 0.32 g of 5,8 - dihydro - 6 - ethoxycarbonyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine, 2.6 g of dimethylformamide, 1.1 g of ethyl iodide and 2 ml of a 20% aqueous solution of potassium carbonate were treated as in Example 13 to give 0.30 g of 5,8 - dihydro - 6 - ethoxycarbonyl - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 144.5—145°C.

EXAMPLE 15

(Example of interconversion by alkylation).

A mixture of 100 mg of 5,8 - dihydro - 6 - ethoxycarbonyl - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine, 1.0 g of dimethylformamide, 300 ml. of ethyl iodide and 1 ml of a 20% aqueous solution of potassium carbonate were treated as in Example 13. The reaction product was recrystallised from acetone-n-hexane to give 82 mg of 5,8 - dihydro - 6 - ethoxycarbonyl - 8 - ethyl - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 147—149°C.

EXAMPLE 16

(Example of interconversion by alkylation).

6 - Carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (7.0 g) was dissolved in a 4% aqueous solution of potassium hydroxide, and after addi-

tion of 5.0 g of diethyl sulphate, the solution was vigorously stirred at room temperature for 2 hours. After having been left to stand overnight, the reaction product was acidified with acetic acid. The precipitated crystals were recovered by filtration, washed with water, and recrystallised from methanol to give 7.2 g of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 253—256°C.

EXAMPLE 17

(Example of interconversion by alkylation).

6 - Carboxy - 5,8 - dihydro - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine (100 mg) was dissolved in 5 ml of a 4% aqueous solution of potassium hydroxide, and, after addition of diethyl sulphate, the solution was treated as in Example 16. The resulting product was recrystallised from chloroform-acetone to give 98 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 254—256°C.

EXAMPLE 18

(Example of interconversion by alkylation).

6 - Carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (1.54 g) was dissolved in 30 ml of a 4% aqueous solution of potassium hydroxide. 2 grams of dimethyl sulphate were added to the resulting solution while cooling, and the mixture was stirred for 4 hours. After having been left to stand overnight, the product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from a large quantity of methanol-chloroform. There was obtained 1.10 g of 6 - carboxy - 5,8 - dihydro - 8 - methyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 299—302°C.

EXAMPLE 19

(Example of interconversion by alkylation with simultaneous saponification).

5,8 - Dihydro - 6 - ethoxycarbonyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (200 mg) was suspended in 10 ml of ethanol-water (1 : 1) containing 0.4 g of potassium hydroxide, and, after addition of 500 mg of diethyl sulphate, the suspension was stirred for 4 hours while cooling. After having been left to stand overnight, the product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from chloroform to give 108 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido - [2,3-d] pyrimidine having a melting point of 253—255°C.

EXAMPLE 20

(Example of interconversion by alkylation).

The following compounds were obtained by the method of Example 19.

(1) 6 - Carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxo - 8 - n - propylpyrido [2,3-d] pyrimidine having a melting point of 197—199°C.

(2) 8 - n - Butyl - 6 - carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 174—176°C.

(3) 6 - Carboxy - 5,8 - dihydro - 8 - isopropyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 231—233°C.

EXAMPLE 21

(Example of interconversion by hydrolysis).

5,8 - Dihydro - 6 - ethoxycarbonyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (20.0 g) was added to 200 ml of a 7% aqueous solution of sodium hydroxide, and the solution was heated for 20 minutes at 100°C. The product was acidified with acetic acid. The precipitated crystals were recovered by filtration and recrystallised from a great quantity of methanol to give 12.5 g of 6 - carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 279—281°C.

EXAMPLE 22

(Example of interconversion by hydrolysis).

5,8 - Dihydro - 6 - ethoxycarbonyl - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine (400 mg) was added to 8 ml of a 5% aqueous solution of sodium hydroxide, and the solution was heated for 15 minutes at 90°C. The resulting product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from a great quantity of methanol-acetone to give 290 mg of 6 - carboxy - 5,8 - dihydro - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of above 250°C.

EXAMPLE 23

(Example of interconversion by hydrolysis).

5,8 - Dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine (1.2 g) was added to 15 ml of a 10% aqueous solution of sodium hydroxide, and the solution was heated for 1 hour and 30 minutes at 125°C. The resulting product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from ethanol to give 0.77 g of 6 - carboxy - 5,8 - dihydro - 2,4 - dimethyl - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 222—224°C.

EXAMPLE 24

(Example of interconversion by hydrolysis).

5,8 - Dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 5 - oxopyrido [2,3-d] pyrimidine (165 mg) was added to 8 ml of a 10% aqueous solution of sodium hydroxide, and the solution was heated for 1 hour and 30 minutes at 120—130°C. The resulting product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from ethanol to give 109 mg of 6 - carboxy - 5,8 - dihydro - 2,4 - dimethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 267—268°C. On admixture of this compound with the starting material, a depression of the melting point of about 20°C was observed.

EXAMPLE 25

(Example of interconversion by hydrolysis).

6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (47 mg) was added to 1 ml of a 5% caustic soda solution, and the mixture was heated for 15 minutes at 90—95°C. After cooling, the resulting product was acidified with acetic acid. The precipitated crystals were recovered by filtration and recrystallised from a large quantity of ethanol to give 31 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - hydroxy - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 287—292°C.

EXAMPLE 26

(Example of inter-conversion by hydrolysis).

5.8 - Dihydro - 6 - ethoxycarbonyl - 8 - ethyl - 2 - methoxy - 5 - oxopyrido [2,3-d] pyrimidine (50 mg) was added to 1 ml of a 5% caustic soda solution, and the mixture was heated for 5 minutes at 95°C. Subjection of the resulting product to the same treatment as in Example 25 gave 33 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - hydroxy - 5 - oxopyrido [2,3-d] pyrimidine.

EXAMPLE 27

(Example of interconversion by hydrolysis).

5,8 - Dihydro - 6 - ethoxycarbonyl - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (200 mg) was added to 4 ml of a 5% caustic soda solution, and the mixture was heated for 15 minutes at 90—95°C. Subjection of the resulting product to the same treatment as in Example 25 gave 123 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - hydroxy - 5 - oxopyrido [2,3-d] pyrimidine.

EXAMPLE 28

(Example of interconversion by hydrolysis).

500 mg. of 5,8 - dihydro - 6 - ethoxycarbonyl - 4 - hydroxy - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine was added to 10 ml of a 7% caustic soda solution, and the mixture was heated for 13 minutes at 90°C for hydrolysis. The product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from methanol-chloroform to give 370 mg of 6 - carboxy - 5,8 - dihydro - 4 - hydroxy - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 287—289°C.

EXAMPLE 29

(Example of interconversion by hydrolysis).

5,8 - Dihydro - 2 - dimethylamino - 6 - ethoxycarbonyl - 5 - oxopyrido [2,3-d] pyrimidine (7.0 g) was added to 100 ml of a 7% caustic soda solution, and the mixture was heated for 30 minutes at 140°C. for hydrolysis. The product was acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from acetonitrile. There were obtained 5.6 g of 6 - carboxy - 5,8 - dihydro - 2 - dimethylamino - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 300—303°C.

EXAMPLE 30

Example of interconversion of a compound of formula (IV) by amination into another compound of formula (IV)).

700 mg. of 5,8 - dihydro - 6 - ethoxycarbonyl - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine were added to 30 ml of absolute ethanol containing 2 g of N,N-dimethylamine, and the mixture was heated in a sealed tube for 6 hours at 95°C. The solvent was removed by distillation, and the residue was recrystallised from ethanol. There were obtained 560 mg of 5,8 - dihydro - 2 - dimethylamino - 6 - ethoxycarbonyl - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 163—164.5°C.

EXAMPLE 31

(Example of interconversion by amination).

700 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine were treated in the same manner as in Example 30. There were obtained 530 mg of 6 - carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 288—291°C.

EXAMPLE 32

(Example of interconversion by amination).

150 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d]pyrimidine was added to 30 ml of absolute ethanol. Into this mixture was dissolved 2.0 g of methylamine, and the solution was heated for 7 hours at 105°C. in a sealed tube. The solvent was removed by distillation, and the residue was washed with ethanol and recrystallised from methanol-chloroform. There was obtained 120 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylamino - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 274—276° C.

When the same procedure was followed using n-butylamine, n-hexylamine, isopropylamine, cyclohexylamine, ethanolamine, diethylaminopropylamine, dimethylaminopropylamine and ethylamine in place of methylamine, the following compounds were obtained.

(1) 2 - N - butylamino - 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine (126 mg; m.p. 192—194°C.)

(2) 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - n - hexylamino - 5 - oxopyrido [2,3-d] pyrimidine (137 mg; m.p. 164—166°C.)

(3) 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - isopropylamino - 5 - oxopyrido [2,3-d] pyrimidine (124 mg; m.p. 233—235°C.)

(4) 6 - Carboxy - 2 - cyclohexylamino - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine (131 mg; m.p. 209—211°C.)

(5) 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - (2 - hydroxyethyl)amino - 5 - oxopyrido [2,3-d] pyrimidine (118 mg; m.p. 268 0 270°C.)

(6) 6 - Carboxy - 2 - [3 - (diethylamino) propylamino] - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine (142 mg; m.p. 160—162°C.)

(7) 6 - Carboxy - 5,8 - dihydro - 2 - [3 - (dimethylamino) propylamino] - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine (135 mg; m.p. 165—167°C.)

(8) 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - ethylamino - 5 - oxopyrido [2,3-d] pyrimidine (107 mg; m.p. 269—272°C.)

EXAMPLE 33

(Example of interconversion by amination).

200 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine were added to 30 ml of absolute ethanol containing 1.2 g of ammonia, and the mixture was reacted for 5.5 hours at 105°C. in a sealed tube. The solvent was removed by distillation, and the residue was recrystallised from ethanol to give 127 mg of 2 - amino - 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 291—293°C.

EXAMPLE 34

(Example of intercoversion by amination).

150 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine was added to 30 ml of absolute ethanol containing 1.1 g of dissolved piperidine, and the mixture was reacted for 5 hours at 95°C. in a sealed tube. The solvent was removed by distillation, and the residue was recrystallised from methanol-chloroform. There were obtained 112 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl -

5 - oxo - 2 - piperidinopyrido [2,3-d] pyrimidine having a melting point of 267—270°C.

EXAMPLE 35

(Example of interconversion by amination).

When morpholine was used instead of piperidine in Example 34, there was obtained 121 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - morpholino - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 270—272°C.

EXAMPLE 36

(Example of interconversion by amination).

When pyrrolidine was used instead of piperidine in Example 34, there were obtained 111 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxo - 2 - pyrrolidinopyrido [2,3-d] pyrimidine having a melting point of 314—316°C.

EXAMPLE 37

(Example of interconversion by amination).

Two hundred milligrams of 6 - carboxy - 5,8 - dihydro - 8 - methyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine was suspended in 30 ml of absolute ethanol containing 6 g of dimethylamine, and the suspension was reacted for 6 hours at 105°C. in a sealed tube. The product was filtered. The solvent was removed by distillation from the filtrate, and the residue was recrystallised from chloroform-methanol. There was obtained 124 mg of 6 - carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - methyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 312—315°C.

EXAMPLE 38

(Example of interconversion by amination).

The following compounds were obtained in the same manner as in Example 37.

(1) 8 - n - Butyl - 6 - carboxy - 5,8 - dihydro - 2 - dimethylamino - 5 - oxypyrido [2,3-d] pyrimidine having a melting point of 205—207°C.

(2) 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 5 - oxo - 8 - n - propylpyrido [2,3-d] pyrimidine having a melting point of 261—262°C.

(3) 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - isopropyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 251—253°C.

EXAMPLE 39

(Example of interconversion by amination)

200 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine and 100 mg of hydrazine were added to 40 ml of ethanol, and the mixture was heated for 15 minutes under reflux. The precipitated crystals were recovered by filtration, and after washing with ethanol, they were suspended in water. Three to five drops of a 10% hydrochloric acid solution were added to the suspension, and the crystals were dissolved. The resulting solution was filtered. The filtrate was made alkaline with potassium carbonate, and then acidified with acetic acid. The precipitated crystals were recovered by filtration, and recrystallised from methanol. There were obtained 121 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - hydrazino - 5 - oxopyrido [2,3-d] pyridine having a melting point of 259—261°C.

EXAMPLE 40

(Example of interconversion by amination).

6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine (200 mg) and 1.0 g of dodecylamine were added to 30 ml. of ethanol, and the mixture was reacted for 6 hours at 105°C. in a sealed tube. At the end of the reaction, the solvent was removed by distillation, and the residue was recrystallised from ethanol. There were obtained 285 mg of a dodecylamine salt of 6 - carboxy - 5,8 - dihydro - 2 - dodecylamino - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 160—163°C.

EXAMPLE 41

(Example of interconversion by amination).

200 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine and 1.0 g of octadecylamine were added to 30 ml of ethanol, and the mixture was reacted for 6.5 hours at 105°C. in a sealed tube. The solvent was removed by distillation, and the residue was recrystallised from ethanol to give 347 mg of an octadecylamine salt of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - octadecylamino - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 160—163°C.

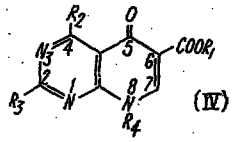
EXAMPLE 42

(Example of interconversion by desulphurisation).

700 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine was dissolved in 300 ml of dioxane, and after addition of 4 g of Raney nickel (W-4), the solution was refluxed for 3 hours. At the end of the reaction, the Raney nickel was separated by filtration. The filtrate was distilled and the residue was recrystallised from ethanol to give 420 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 219—222°C.

WHAT WE CLAIM IS:—

1. 5,8-Dihydro-5-oxopyrido [2,3-d] pyrimidine derivatives of general formula:



(IV)

wherein R_1 stands for hydrogen or a lower alkyl radical; R_2 stands for hydrogen, a lower alkyl radical, a hydroxy group, a halogen atom, a lower alkoxy radical, an amino group or a lower alkylthio radical; R_3 stands for hydrogen, a lower alkyl radical, a hydroxy group, a lower alkoxy radical, a lower alkylthio radical or a radical of formula

$$-N<\begin{matrix}R'\\R''\end{matrix}$$

(R′ standing for hydrogen, an alkyl radical, a cycloalkyl radical, an amino group, a hydroxyalkyl radical or an alkyl-substituted aminoalkyl radical, and R″ for hydrogen or an alkyl radical, or R′ and R″, together with the nitrogen atom to which they are bonded, forming a heterocyclic ring); and R_4 stands for hydrogen or an alkyl radical.

2. Compounds according to claim 1, wherein R_2 is a hydrogen atom, a lower alkyl radical, a hydroxy group or a halogen atom.

3. Compounds according to claim 1 or 2, wherein R_1 is a hydrogen atom and R_4 is an alkyl radical.

4. Compounds according to claim 1 or 2, wherein R_1 is a hydrogen atom or a lower alkyl radical, R_3 is a lower alkylthio radical or a radical of formula

$$-N<\begin{matrix}R'\\R''\end{matrix}$$

(R′ and R″ being as defined in claim 1), and R_4 is an alkyl radical.

5. Compounds according to any preceding claim, wherein R_4 is a lower alkyl radical.

6. Organic amine salts of compounds according to any preceding claim, wherein R_1 is a hydrogen atom.

7. Compounds according to claim 1 or 6, substantially as herein described.

8. Compounds according to claim 1, wherein R_1 is a lower alkyl radical, R_2 is a hydrogen atom or a lower alkyl radical, R_3 is a lower alkyl, lower alkoxy or lower alkylthio radical and R_4 is a hydrogen atom.

9. Compounds according to claim 8, substantially as herein described.

10. Compounds according to claim 1, wherein R_1 is a hydrogen atom or a lower alkyl radical, R_2 is a hydrogen atom or a lower alkyl radical, R_3 is a lower alkyl, lower alkoxy or lower alkylthio radical.

11. Compounds according to claim 10, substantially as herein described.

12. Compounds according to claim 1, wherein R_1 is a hydrogen atom or a lower alkyl radical, R_2 is a hydrogen atom, R_3 is a lower alkylthio radical or a radical of formula

$$-N<\begin{matrix}R'\\R''\end{matrix}$$

(R′ and R″ both representing a hydrogen atom or a lower alkyl group, or R′ and R″ together with the nitrogen atom to which they are attached forming a heterocyclic ring), and R_4 is a lower alkyl radical.

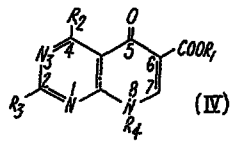
EXAMPLE 42

(Example of interconversion by desulphurisation).

700 mg. of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d] pyrimidine was dissolved in 300 ml of dioxane, and after addition of 4 g of Raney nickel (W-4), the solution was refluxed for 3 hours. At the end of the reaction, the Raney nickel was separated by filtration. The filtrate was distilled and the residue was recrystallised from ethanol to give 420 mg of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d] pyrimidine having a melting point of 219—222°C.

WHAT WE CLAIM IS:—

1. 5,8-Dihydro-5-oxopyrido [2,3-d] pyrimidine derivatives of general formula:



(IV)

wherein R_1 stands for hydrogen or a lower alkyl radical; R_2 stands for hydrogen, a lower alkyl radical, a hydroxy group, a halogen atom, a lower alkoxy radical, an amino group or a lower alkylthio radical; R_3 stands for hydrogen, a lower alkyl radical, a hydroxy group, a lower alkoxy radical, a lower alkylthio radical or a radical of formula

$$-N<^{R'}_{R''}$$

(R' standing for hydrogen, an alkyl radical, a cycloalkyl radical, an amino group, a hydroxyalkyl radical or an alkyl-substituted aminoalkyl radical, and R'' for hydrogen or an alkyl radical, or R' and R'', together with the nitrogen atom to which they are bonded, forming a heterocyclic ring); and R_4 stands for hydrogen or an alkyl radical.

2. Compounds according to claim 1, wherein R_2 is a hydrogen atom, a lower alkyl radical, a hydroxy group or a halogen atom.

3. Compounds according to claim 1 or 2, wherein R_1 is a hydrogen atom and R_4 is an alkyl radical.

4. Compounds according to claim 1 or 2, wherein R_1 is a hydrogen atom or a lower alkyl radical, R_3 is a lower alkylthio radical or a radical of formula

$$-N<^{R'}_{R''}$$

(R' and R'' being as defined in claim 1), and R_4 is an alkyl radical.

5. Compounds according to any preceding claim, wherein R_4 is a lower alkyl radical.

6. Organic amine salts of compounds according to any preceding claim, wherein R_1 is a hydrogen atom.

7. Compounds according to claim 1 or 6, substantially as herein described.

8. Compounds according to claim 1, wherein R_1 is a lower alkyl radical, R_2 is a hydrogen atom or a lower alkyl radical, R_3 is a lower alkyl, lower alkoxy or lower alkylthio radical and R_4 is a hydrogen atom.

9. Compounds according to claim 8, substantially as herein described.

10. Compounds according to claim 1, wherein R_1 is a hydrogen atom or a lower alkyl radical, R_2 is a hydrogen atom or a lower alkyl radical, R_3 is a lower alkyl, lower alkoxy or lower alkylthio radical.

11. Compounds according to claim 10, substantially as herein described.

12. Compounds according to claim 1, wherein R_1 is a hydrogen atom or a lower alkyl radical, R_2 is a hydrogen atom, R_3 is a lower alkylthio radical or a radical of formula

$$-N<^{R'}_{R''}$$

(R' and R'' both representing a hydrogen atom or a lower alkyl group, or R' and R'' together with the nitrogen atom to which they are attached forming a heterocyclic ring), and R_4 is a lower alkyl radical.

* C L M S *

13. Compounds according to claim 12, substantially as herein described.

14. Compounds according to claim 1, wherein R_1 is a hydrogen atom or a lower alkyl group, R_2 is a hydrogen atom, R_3 is a lower alkylthio or lower alkoxy radical, or a hydroxy group and R_4 is a lower alkyl radical.

15. Compounds according to claim 14, wherein R_1 is a hydrogen atom and R_3 is a hydroxy group.

16. Compounds according to claim 14, substantially as herein described.

17. 5,8 - Dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 5 - oxopyrido[2,3-d] pyrimidine.

18. 5,8 - Dihydro - 6 - ethoxycarbonyl - 2 - methylthio - 5 - oxopyrido[2,3-d] pyrimidine.

19. 5,8 - Dihydro - 6 - ethioxycarbonyl - 8 - ethyl - 2 - methylthio - 5 - oxopyrido[2,3-d]pyrimidine.

20. 5,8 - Dihydro - 6 - ethoxycarbonyl - 2 - methoxy - 5 - oxopyrido[2,3-d] pyrimidine.

21. 5,8 - Dihydro - 6 - ethoxycarbonyl - 8 - ethyl - 2 - methoxy - 5 - oxopyrido [2,3-d]pyrimidine.

22. 5,8 - Dihydro - 2 - dimethylamino - 6 - ethoxycarbonyl - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine.

23. 5,8 - Dihydro - 6 - ethoxycarbonyl - 2 - hydroxy - 5 - oxopyrido[2,3-d] pyrimidine.

24. 5,8 - Dihydro - 2,4 - dimethyl - 6 - ethoxycarbonyl - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine.

25. 5,8 - Dihydro - 2 - dimethylamino - 6 - ethoxycarbonyl - 5 - oxopyrido-[2,3-d]pyrimidine.

26. 5,8 - Dihydro - 6 - ethoxycarbonyl - 4 - hydroxy - 2 - methylthio - 5 - oxopyrido[2,3-d]pyrimidine.

27. 6 - Carboxy - 5,8 - dihydro - 2,4 - dimethyl - 8 - ethyl - 5 - oxopyrido [2,3-d]pyrimidine.

28. 6 - Carboxy - 5,8 - dihydro - 2,4 - dimethyl - 5 - oxopyrido[2,3-d]' pyrimidine.

29. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - hydroxy - 5 - oxopyrido[2,3-d] pyrimidine.

30. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylthio - 5 - oxopyrido [2,3-d]pyrimidine.

31. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methylamino - 5 - oxopyrido [2,3-d]pyrimidine.

32. 2 - Amino - 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido[2,3-d] pyrimidine.

33. 6 - Carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxopyrido[2,3-d] pyrimidine.

34. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - methoxy - 5 - oxopyrido [2,3-d]pyrimidine.

35. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - morpholino - 5 - oxopyrido [2,3-d]pyrimidine.

36. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxo - 2 - piperidino - pyrido [2,3-d]pyrimidine.

37. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - (2 - hydroxyethyl)amino - 5 - oxopyrido[2,3-d]pyrimidine.

38. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxo - 2 - pyrrolidino - pyrido [2,3-d]pyrimidine.

39. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - isopropylamino - 5 - oxopyrido [2,3-d]pyrimidine.

40. 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - ethyl - 5 - oxopyrido [2,3-d]pyrimidine.

41. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine.

42. 6 - Carboxy - 2 - cyclohexylamino - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d]pyrimidine.

43. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - n - hexylamino - 5 - oxopyrido [2,3-d]pyrimidine.

44. 2 - n - Butylamino - 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido [2,3-d]pyrimidine.

45. 6 - Carboxy - 2 - [3 - (diethylamino)propylamino] - 5,8 - dihydro - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine.

* C L M S *

46. 6 - Carboxy - 5,8 - dihydro - 2[3 - (dimethylamino)propylamino] - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine.

47. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - ethylamino - 5 - oxopyrido [2,3-d]pyrimidine.

48. 6 - Carboxy - 5,8 - dihydro - 8 - methyl - 2 - methylthio - 5 - oxopyrido [2,3-d]pyrimidine.

49. 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - methyl - 5 - oxopyrido [2,3-d]pyrimidine.

50. 6 - Carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxo - 8 - n - propyl - pyrido[2,3-d]pyrimidine.

51. 8 - n - Butyl - 6 - carboxy - 5,8 - dihydro - 2 - methylthio - 5 - oxopyrido [2,3-d]pyrimidine.

52. 6 - Carboxy - 5,8 - dihydro - 8 - isopropyl - 2 - methylthio - 5 - oxopyrido [2,3-d]pyrimidine.

53. 8 - n - Butyl - 6 - carboxy - 5,8 - dihydro - 2 - dimethylamino - 5 - oxo-pyrido[2,3-d]pyrimidine.

54. 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 5 - oxo - 8 - n - propyl - pyrido[2,3-d]pyrimidine.

55. 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 8 - isopropyl - 5 - oxo-pyrido[2,3-d]pyrimidine.

56. 6 - Carboxy - 5,8 - dihydro - 8 - ethyl - 2 - hydrazino - 5 - oxopyrido [2,3-d]pyrimidine.

57. The dodecylammonium salt of 6 - carboxy - 5 - 8 - dihydro - 2 - doceyl-amino - 8 - ethyl - 5 - oxopyrido[2,3-d]pyrimidine.

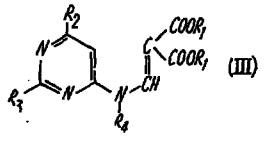
58. The octadecylammonium salt of 6 - carboxy - 5,8 - dihydro - 8 - ethyl - 2 - octadecylamino - 5 - oxopyrido[2,3-d]pyrimidine.

59. 6 - Carboxy - 5,8 - dihydro - 4 - hydroxy - 2 - methylthio - 5 - oxopyrido [2,3-d]pyrimidine.

60. 6 - Carboxy - 5,8 - dihydro - 2 - dimethylamino - 5 - oxopyrido[2,3-d] pyrimidine.

61. 6 - Carboxy - 5,8 - dihydro - 2 - methoxy - 5 - oxopyrido[2,3-d]pyrimidine.

62. Process for the production of a 5,8 - dihydro - 5 - oxopyrido[2,3-d]pyrimidine derivative claimed in any one of claims 1 to 5 which comprises heating an N - (6 - pyrimidinyl)aminomethylenemalonic acid or ester of formula:

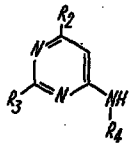

(III)

(wherein R_1, R_2, R_3, and R_4 are as defined in the said claim).

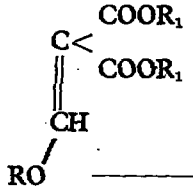
63. Process according to claim 62, wherein the compound of formula (III) is one in which R_1, R_2, R_3 and R_4 are as defined in claim 8.

64. Process according to claim 62 or 63, wherein the compound of formula (III) is heated under reflux in an inert organic solvent which boils at 100°C—300°C.

65. Process according to any one of claims 62 to 64, wherein the compound of formula (III) has been produced by a process which comprises reacting a 6-aminopyrimidine compound of formula:


(I)

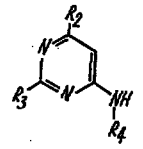
with an alkoxymethylenemalonic acid or ester of formula


(II)

(wherein R represents a lower alkyl radical, and R_1, R_2, R_3 and R_4 are as defined in the said claim).

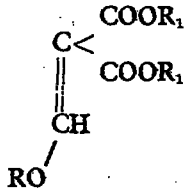
66. Process according to claim 65, wherein the reaction is carried out by heating at 80—150°C.

67. Process according to claim 63, wherein the compound of formula (III) has been produced by a process which comprises reacting a 6-aminopyrimidine compound of formula:



(I)

with an alkoxymethylenemalonic acid or ester of formula



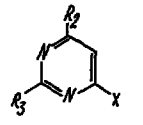
(II)

(wherein R represents a lower alkyl radical and R_1, R_2, R_3 and R_4 are as defined in claim 8).

68. Process according to claim 63, substantially as described in Example 7 or 8.

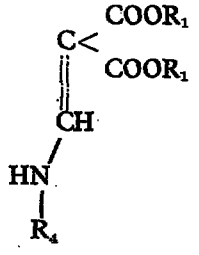
69. Process according to claim 67, substantially as described in Examples 1 and 7 or 2 and 8.

70. Process according to any of claims 62 to 64 wherein the compound of formula (III) has been produced by a process which comprises reacting a 6-halogeno pyrimidine compound of formula:



(I')

with an aminomethylenemalonic acid or ester of formula



(II')

(wherein X is a halogen atom and R_1, R_2, R_3 and R_4 are as defined in the said claim).

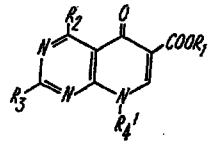
71. Process according to claim 70, wherein the reaction is carried out by heating at 80—150°C. in an inert solvent.

72. Process according to claim 70, substantially as herein described, with reference to Example 6.

73. Process according to claim 62, substantially as herein described.

74. Process for producing a 5,8 - dihydro - 5 - oxopyrido[2,3-d]pyrimidine derivative of the formula given in claim 1, wherein R_1 is hydrogen, which comprises subjecting to acid or alkaline hydrolysis a compound of formula:

* C L M S *



wherein R_1, R_2, R_3 and R_4, are as defined in claim 1, provided that if R_1 represents a hydrogen atom, R_4 is an alkyl radical and R_3 is a lower alkoxy or lower alkylthio radical or a radical of formula

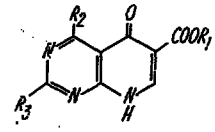
$$-N<\begin{matrix}R'\\R''\end{matrix}$$

(R' and R'' being as defined in claim 1) which is replaced by a hydroxy group in the resulting product.

75. Process according to claim 74, in which the compound hydrolysed is of the formula shown in claim 74, wherein R_1 and R_3 are the same or different lower alkyl radicals and R_4 is hydrogen.

76. Process according to claim 74, wherein the compound hydrolysed is of the formula shown in claim 74, wherein R_3 is a lower alkoxy or lower alkylthio radical and R_4 is a lower alkyl radical.

77. A process for producing a 5,8 - dihydro - 5 - oxopyrido[2,3-d]pyrimidine derivative of formula given in claim 1 wherein R_4 is an alkyl radical which comprises reacting a compound of formula:

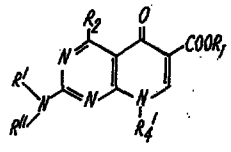


wherein R_1, R_2 and R_3 are as defined in claim 1, with an alkylating agent.

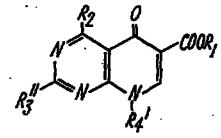
78. Process according to claim 77, wherein the reaction is carried out in the presence of an alkali.

79. Process according to claim 77 or 78, in which the compound alkylated is of the formula shown in claim 77, wherein R_2 is a hydrogen atom or a lower alkyl radical and R_3 is a lower alkyl, lower alkoxy or lower alkylthio radical.

80. Process for producing a 5,8-dihydro-5-oxopyrido[2,3-d]pyrimidine derivative of formula:



wherein R_1, R_2, R' and R'' are as defined in claim 1 and R'_4 is an alkyl radical, which comprises reacting a compound of formula:



wherein R_1 and R_2 are as defined in claim 1, R''_3 is a lower alkoxy or lower alkylthio radical and R'_4 is an alkyl radical, with an amine of formula

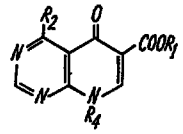
* C L M S *

$$H<\begin{matrix}R'\\R''\end{matrix},$$

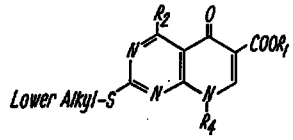
R′ and R″ being as defined above.

81. Process according to claim 80, in which the compound to be reacted with the amine is of the second formula given in claim 80, wherein R_2 is a hydrogen atom, R_3 is a lower alkylthio radical and R'_4 is a lower alkyl radical.

82. Process for producing a 5,8-dihydro-5-oxopyrido[2,3-d]pyrimidine derivative of formula:



wherein R_1, R_2 and R_4 are as defined in claim 1 which comprises heating a compound of the formula:



with Raney nickel.

83. Compounds according to claim 1 when prepared by a process claimed in any one of claims 62 to 82.

84. Compounds according to claim 1 when prepared by a process claimed in claim 63, 67, 68 or 70.

85. Compounds according to claim 1 when prepared by a process claimed in claim 75.

86. Compounds according to claim 1 when prepared by a process claimed in claim 76.

87. Compounds according to claim 1 when prepared by a process claimed in claim 79.

88. Compounds according to claim 1 when prepared by a process claimed in claim 81.

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