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COMPLETE SPECIFICATION

Novel D-Threo-1-Phenyl-2-Aminopropan-1,3-Diol Derivatives and a process for their production

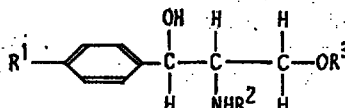
We, BIOCHEMIE GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, an Austrian Company, of Kundl, Austria, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives and methods for preparing them.

The antibiotic chloramphenicol and certain analogous compounds command considerable interest for the treatment of bacterial infections. The majority of these antibiotics are administered orally. For parenteral, that is to say intramuscular or intravenous, administration, water-soluble derivatives have been developed among which chloramphenicol succinate sodium has been therapeutically used to some extent. This preparation is commercially sold in a dry substance ampoule containing the chloramphenicol monosuccinate sodium in the form of a lyophilized hygroscopic dry powder together with an ampoule aq.bidest. which is required for the preparation of an injectable solution. At normal temperature the prepared aqueous solution does not keep long.

It is an object of the present invention to provide derivatives of chloramphenicol and its analogues which possess valuable pharmaceutical properties. It is another object of the invention to provide novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives providing prolonged blood level value of the antibiotic agent. It is a further object of the invention to produce novel antibiotic agents which are characterised by their excellent antibiotic activity and high compatibility. It is still another object of the present invention to provide novel antibiotic agents, which are stable in aqueous solution or suspension, and which can be sold in the form of aqueous preparations that will keep.

The novel compounds according to the present invention are D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives of the general formula



(I)

in which formula the *p*-position of the phenyl group (R¹) and the amino group of the amino-propanediol (R²) bear specific substituents which agree with those of chloramphenicol or which differ from them. Thus, in the above general formula R¹ represents hydrogen, an NO₂—, CN—, CH₂SO₂—, CH₂S—, NH₂— or XCONH— group or a halogen atom, preferably Cl, X being the dichloromethyl, azidomethyl, benzyl, phenoxyethyl, phenyl or isopropyl radical; R² represents an XCO group, wherein X has the above stated meaning, R² preferably being the Cl₂CHCO— or N₃CH₂CO—

[Price 4s. 6d.]

group; and R³ represents a carbamidocarboxylic acid or a carbamidocarboxylic acid ester radical, preferably a radical of formula III:—



wherein R⁴ is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms, an alkyl radical having an interposed hetero-atom, e.g. sulphur, and containing up to 6 carbon atoms, a carbalkoxy or carbalkoxyalkyl radical or an aryl radical, R⁵ is an alkyl radical having up to 4 carbon atoms or hydrogen and X¹ is a direct C—C bond or a —(CH₂)_n—grouping in which n is an integer from 1 to 6.

The present invention also includes the salts of acids of general formula I with inorganic or organic bases.

Experiments have disclosed that chloramphenicol succinate solutions completely decompose when they are heated at 120°C for one hour, whereas similarly treated solutions or suspensions of D-threo-1-phenyl-2-amino-propan-1,3-diol carbamidocarboxylates or carboxylic acids of general formula I or their salts remain unchanged. From solutions or suspensions thus treated the reactive agent can be recovered quantitatively. Although the novel compounds are inactive in vitro they develop their full activity in vivo as illustrated by the following tests.

Blood level tests were performed on rabbits. Ten rabbits were used for the experiments and were intramuscularly injected with an aqueous solution of the sodium salt of chloramphenicol carbamidoacetic acid, corresponding to 75 mg/kg of chloramphenicol. The results obtained are listed in Table 1. The animals accepted the injections without any signs of pain or other secondary effects. For the determination of blood level, samples of the animals' blood were taken at the end of the times shown in Table 1 and the antibiotic activity was determined by reference to a chloramphenicol standard in a series dilution test with the test organism *Staphylococcus aureus* SG 511.

TABLE 1

after	Blood level values (in γ/ml)					
	30 min.	1 h	2 h	4 h	8 h	24 h
Mean value (10 tested animals)	13.00	13.00	16.00	17.00	7.75	8.75
Scatter	3.50	3.50	3.16	2.58	0.79	1.32

From the blood level tests it appears that the substance is quantitatively split in vivo.

The toxicity of this compound is perceptively lower than that of chloramphenicol monosuccinate, as borne out by the following comparative data:—

LD ₅₀ (subcutaneous in white mice)	
sodium salt of chloramphenicol-carbamidoacetic acid	7400 mg/kg
Chloramphenicol monosuccinate sodium	1850 mg/kg

In tests on humans the novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives, such as the sodium salt of chloramphenicol carbamidoisocaproic acid, proved to be perceptibly superior to the known chloramphenicol compounds or its analogues, such as chloramphenicol monosuccinate, both in relation to the height and/or the duration of the blood level values.

After oral administration in animal tests the novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives were found to be readily resorbed and to have a distinct depot effect when compared with chloramphenicol and its analogues. The effect that can be achieved is illustrated by comparative tests which gave the results collated in Tables 2 to 4.

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TABLE 2

Blood level values in γ /ml after oral administration of 75 mg/kg of chloramphenicol in rabbits

after	Blood level values (in γ /ml)				
	1 h	2 h	4 h	8 h	24 h
Mean value (10 tested animals)	25.50	23.00	18.50	13.50	8.25
Scatter	10.92	11.11	7.09	3.37	1.21

TABLE 3

Blood level values in γ /ml after oral administration of chloramphenicol carbamidoacetic acid, corresponding to 75 mg/kg chloramphenicol in rabbits

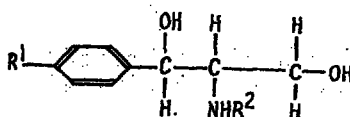
after	Blood levels values (in γ /ml)				
	1 h	2 h	4 h	8 h	24 h
Mean value (5 tested animals)	26.0	18.0	16.0	14.0	13.5
Scatter	15.17	8.37	5.48	4.18	4.87

Table 4 illustratively exemplifies the prolongation of blood level values that can be achieved with two of the chloramphenicol analogue derivatives that are obtainable according to the invention. The compounds were tested in the same way as above. The values given in the Table are mean values obtained when testing 5 rabbits.

TABLE 4

Compound (parenteral administration)	Hours				
	1	2	4	8	24
Threo-1- <i>p</i> -nitrophenyl-2-azidoacetylaminopropan-1,3-diol-3-carbamidoacetic acid	8.5	9.0	9.0	6.5	6.0
Threo-1- <i>p</i> -nitrophenyl-2-azidoacetylaminopropan-1,3-diol-carbamidoisocaproic acid	8.5	9.5	8.5	7.5	7.5
(Comparison) Threo-1- <i>p</i> -nitrophenyl-2-azidoacetylaminopropan-1,3-diol	9.5	8.5	8.0	4.5	3.0

According to the invention the novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives and the salts of the corresponding acids are obtained by reacting a compound of the general formula II

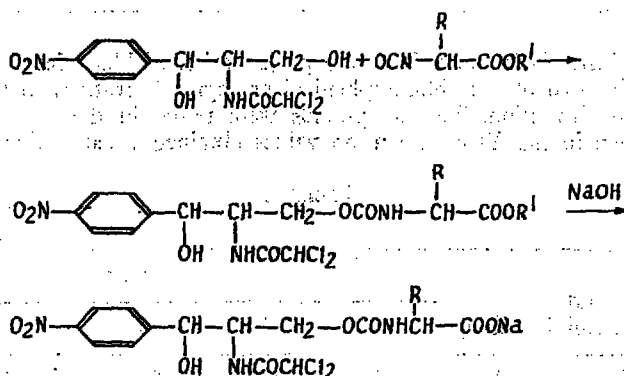


(II)

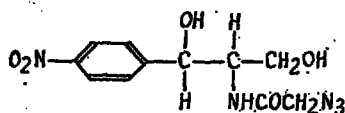
wherein R¹ and R² have the above stated meaning, with an ester of an isocyanato-carboxylic acid to obtain the corresponding D-threo-1-phenyl-2-amino-propan-1,3-diol carbamidocarboxylate ester, and, if the free acid is required, saponifying the ester to the corresponding carbamidocarboxylic acid and, if a salt of the acid is desired, salifying the resultant acid with an inorganic or organic base.

The method according to the invention is based on the reaction of esters of isocyanatocarboxylic acids with the primary hydroxyl group of the D-threo-phenyl-2-amino-propan-1,3-diol compound of general formula II, causing the formation of the corresponding esters of carbamidocarboxylic acids which can be selectively saponified to the corresponding free acids. It was initially uncertain whether in the case of compounds of general formula II this reaction would lead to the formation of uniform products because both primary and secondary hydroxyl groups readily react with esters of isocyanatocarboxylic acids. It is known from the literature (Glazko et al, Antib. Annual 1957/58, 792) that mixtures of mono- and disuccinate were first obtained in the preparation of chloramphenicol succinate. It was also uncertain whether the selective saponification of the ester grouping would be feasible without the dichloroacetyl or the azidoacetyl radical being detached. It was therefore surprising when it was found that compounds of the general formula II react with esters of isocyanatocarboxylic acids primarily at the hydroxyl group and that uniform monoderivatives result. It was also unexpected to find that good yields of the above esters could be selectively saponified to the corresponding acids.

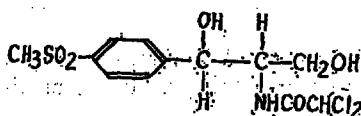
When using chloramphenicol as the starting reactant of general formula II, the method proposed by the invention can be illustratively exemplified by the following reaction scheme:—



Preferred starting reactants of general formula II besides chloramphenicol for performing the method according to the invention are [D(-)-threo-1-*p*-nitrophenyl-2-azidoacetylamidopropan-1,3-diol]



and a 4'-methylsulphonyl analogue of chloramphenicol having the formula



In the performance of the method according to the invention ethyl acetate is conveniently used as the reaction medium. However, the reaction can also be performed in butyl acetate, isobutyl acetate, dioxan, tetrahydrofuran, dimethyl formamide, formamide, acetone, methylisobutylketone, benzene, toluene and other organic solvents.

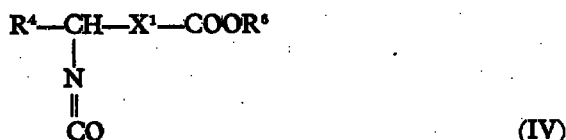
The reaction is accelerated by tertiary bases, such as triethylamine and dimethylaniline as well as pyridine.

Conveniently the reaction is performed at room temperature. In some cases it is advantageous to heat the reaction mixture.

The saponification of the resultant esters to the corresponding acids can be effected with alkali metal hydroxides or carbonates or alkaline earth metal hydroxides or carbonates, as well as with primary, secondary and tertiary amines and hydroxy-alkylamines.

In a manner known to the art water-soluble amine, alkali metal or alkaline earth metal salts, for instance of Na, K, Ca or ammonia, which form stable aqueous solutions, can be prepared from the acids thus obtained. Moreover, organic bases, such as dibenzylamine or derivatives of ethylenediamine, such as dibenzylethylene diamine, likewise permit crystalline salts to be prepared which, owing to their low solubility in water, can be used as products that have a depot effect in the same way as the novel esters of chloramphenicol carbamidocarboxylic acids and the corresponding free acids.

Among the novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives the preferred compounds are obtained by reacting compounds of the general formula II with esters of isocyanatocarboxylic acids of the general formula IV:—



wherein R⁴ and X¹ have the above specified meanings and R⁶ is an alkyl group having up to 4 carbon atoms.

Particular examples of reaction components of this general formula are alkyl esters of α -isocyanatoacetic acid, alkyl esters of α -isocyanato- γ -methylmercaptobutyric acid, alkyl esters of α -isocyanatoisocaproic acid, alkyl esters of α -isocyanatoisovaleric acid, alkyl esters of α -isocyanatopropionic acid, alkyl esters of α -isocyanato (phenyl) acetic acid, dialkyl esters of α -isocyanatoglutaric acid, dialkyl esters of α -isocyanatosuccinic acid and alkyl esters of ϵ -isocyanatocaproic acid.

EXAMPLE 1:—

a) Ethyl-chloramphenicol carbamidoacetate.

323 g (1 mole) of chloramphenicol were suspended in 100 ml of ethyl acetate. 160 ml of pyridine and 129 g (1 mol) of ethyl-isocyanatoacetate were added. By allowing the mixture to stand at room temperature with occasional shaking, solution was completed after a short time. At the end of 3 hours the reaction product began to crystallize in the form of white needles. At the end of another 40 hours the crystal magma was filtered off with suction at room temperature, washed with ether and dried. 325 g of colourless crystals melting at 138 to 140° C were obtained. A further quantity of 53.3 g crystallized from the mother liquor after extraction of the pyridine with dilute hydrochloric acid and concentration of the ethyl acetate solution. The total yield was 83.6% of theory.

Molecular formula:— C₁₆H₁₉O₈N₃Cl₂

Analysis:— Calculated:— C=42.49% H=4.23%
Found:— C=42.69% H=4.39%

The ester could be recrystallized from ethanol, ethyl acetate or acetone.

b) Chloramphenicol carbamido acetic acid.

For saponification 100 g of the ester obtained according to a) were suspended in 30 ml of ethanol. In the course of one hour 115 ml of a 2N solution of sodium hydroxide were added dropwise at room temperature, with stirring. The ester then dissolved. After the solution had been kept standing at room temperature the pH

had dropped to 7. After concentration in vacuo the solution was diluted with water and slowly acidified with dilute hydrochloric acid, causing the acid to crystallize in pure form. When the product had been filtered off, washed with water and dried, 80.7 g of acid (i.e. 86% of theory) melting at 150 to 153° C were obtained. The acid could be recrystallized from water, ethanol, acetone or ethyl acetate.

Molecular formula: — $C_{11}H_{15}N_3O_8Cl_2$

Analysis: — Calculated: — C=39.64% H=3.56%

Found: — C=39.93% H=3.74%

c) The sodium salt of chloramphenicol carbamidoacetic acid.

4.24 g of the acid obtained as described in b) were dissolved in 10 ml of a 1-molar solution of sodium ethyl hexoate in acetone, 100 ml of ether being added. The sodium salt which initially separated in the form of an oil became solid when rubbed. The product was filtered off with suction, washed with ether and dried.

Yield: — 4.5 g (93% of theory); a white non-hygroscopic water-soluble powder. M.p. 120—130°C.

The sodium salt could also be obtained by evaporating aqueous solutions of the sodium salt.

Moreover, the sodium salt could be directly isolated from the saponification mixture (obtained as described under b) by evaporating the saponified neutral solution in vacuo until dry and recrystallizing the residue for purification from a mixture of ethanol and ether.

d). The potassium salt of chloramphenicol carbamidoacetic acid.

The potassium salt could be prepared analogously to c) by using potassium ethyl hexoate or potassium acetate. It is a white non-hygroscopic powder.

e) The calcium salt of chloramphenicol carbamidoacetic acid.

0.79 g of calcium acetate were added to a solution of 4.24 g of chloramphenicol carbamidoacetic acid in 50 ml of ethanol, the solution being stirred for a while and then evaporated in vacuo. The residue was recrystallized from a mixture of ethanol and ether (1:1).

Yield: — 3.9 g (88% of theory); a white, water-soluble powder. M.p. 160 to 165°C.

f) The dibenzylamine salt of chloramphenicol carbamidoacetic acid.

4.24 g of acid (obtained according to b) were dissolved in 30 ml of ethanol and 2 ml of dibenzylamine were added. Water was then added with stirring until the solution became cloudy. The rapidly crystallizing salt was filtered off and dried. It melts between 153 and 156°C and at room temperature its solubility in water is 0.56%. The water content of the solid substance is 0.06%.

g) The dibenzylethylenediamine salt of chloramphenicol carbamidoacetic acid.

A solution of 9 g of the sodium salt (obtained as described in c) in a mixture of 30 ml of ethanol and 30 ml of water was gently warmed and a solution of 3.6 g of dibenzylethylenediamine diacetate, in 20 ml of water was added. When the clear solution was cooled it rapidly crystallized. The crystal magma was filtered off with suction, washed with a little water and dried.

Yield: — 8.7 g (81% of theory) of the dibenzylethylenediamine salt melting between 112 and 116°C. Water content 2.13%. At 28°C its solubility in water is 1.08%.

This salt can also be prepared from the free acid and the free base. The dibenzylethylenediamine salt can also be directly precipitated from saponification mixtures (cf. under b) from an aqueous solution by adding dibenzylethylenediamine acetate solutions.

In a manner analogous to that described in Example I the corresponding esters of chloramphenicolcarbamidocarboxylic acids or the carboxylic acids and their salts were prepared from chloramphenicol and the esters of isocyanatocarboxylic acids named in the Table. Data relating to their chemical and physical properties are shown in Table 5.

TABLE 5

Example No.	Isocyanato-carboxylic acid ester	Chloramphenicol-carbamidocarboxylic acid esters			Chloramphenicol-carbamidocarboxylic acids			Salts of chloramphenicol-carbamidocarboxylic acids	
		M.p. °C:		Analysis	M.p. °C:		Analysis	Salt	M.p. °C.
		C	F		C	F			
a)	b)	c)	d)	e)	f)	g)	h)	i)	j)
2	Methyl-L- α -isocyanato- γ -methylmercaptobutyrate	141 — 172.5	42.20 — 42.50	4.52 — 4.60	141 — 144	40.97 — 40.78	4.25 — 4.03	Sodium salt	
3	Methyl-DL- α -isocyanato- γ -methyl-mercaptobutyrate	115 — 140			132 — 136				
4	Methyl-D- α -isocyanato- γ -methylmercaptobutyrate	145 — 146	42.20 — 42.17	4.52 — 4.64	oily			Sodium salt	
5	Methyl-DL- α -isocyanato-isovalerate		oil			oil		Sodium salt	142 — 144
6	Ethyl-DL- α -isocyanato-propionate	160 — 162			205 — 206	41.11 — 41.31	3.91 — 4.1		
7	Ethyl-L- α -isocyanato(Phenyl)-acetate D-form	176 — 177 121 — 123	49.04 — 48.77	4.11 — 4.27	amorphous			Sodium salt	166 — 170
8	Dimethyl-L- α -isocyanato-glutarate	151 — 152			117 — 125	41.15 — 40.90	3.86 — 3.86		
9	Dimethyl-L- α -isocyanato-succinate	153 — 154	42.36 — 42.25	4.15 — 4.05	oily				
10	Methyl- ϵ -isocyanato-caproate	104 — 106	46.16 — 46.63	5.09 — 5.12	oily				

EXAMPLE 11:—

a) Methyl-L-chloramphenicol-carbamido-isocaproate.

A mixture of 32.3 g (0.1 mol) of chloramphenicol, 16 ml of pyridine and 17.1 g (0.1 mol) of methyl-L-isocyanatoisocaproate were refluxed for 1 hour in 100 ml of ethyl acetate. For removing the pyridine the yellow solution was then extracted with diluted hydrochloric acid, the ethyl acetate solution was dried and evaporated. The

5 remaining oil solidified when rubbed with petroleum ether, yielding 41.3 g of an amorphous material which slowly softened again over 70°C. By recrystallization from an ethyl acetate and petroleum ether mixture 33.5 g of crystallized substance (68% of theory) melting between 124 and 130°C were obtained. For an analysis this was twice recrystallized from dilute ethanol. M.p. = 133—134°C.

Molecular formula: — $C_{19}H_{25}O_8N_3Cl_2$

Analysis: — Calculated: — C = 46.16% H = 5.09%

Found: — C = 46.62% H = 5.19%

b) L-chloramphenicol-carbamidoisocaproic acid.

10 For saponification 20 g of the ester obtained under a) were dissolved in 100 ml of hot ethanol and 26 ml of a 2N-solution of sodium hydroxide were added to the hot solution. At the end of about 1 hour the pH of the yellow solution that had meanwhile formed had dropped to 8.0. This was concentrated and then diluted with water, the resultant cloudiness being removed by extraction with ether. When the solution was acidified an oil precipitated which was extracted with ether. After drying, treating with active carbon and evaporating, 16.3 g (83% of theory) of the amorphous material which slowly softened again over 70°C. By recrystallization from M.p. = 86—88°C.

Molecular formula: — $C_{18}H_{19}O_7N_3Cl_2$

20 Analysis: — Calculated: — C = 45.48% H = 4.83%

Found: — C = 46.10% H = 5.26%

The acid forms an crystalline adduct with ethyl acetate. M.p. 124—127°C.

Molecular formula: — $C_{18}H_{22}O_8N_3Cl_2 \cdot C_4H_8O_2$

25 Analysis: — Calculated: — C = 45.48% H = 4.83%

Found: — C = 46.10% H = 4.87%

c) The sodium salt.

30 In order to prepare the sodium salt the acid was dissolved in water with one equivalent of sodium hydroxide or sodium carbonate or sodium bicarbonate and the solution was evaporated until dry. Acetone was added for purification, the undissolved residue removed by filtration and the filtrate reconcentrated. The sodium salt was thus obtained in the form of a light white powder melting between 135 and 140°C.

d) The dibenzylamine salt.

35 5 g of the acid obtained as described in b) were dissolved in 100 ml of ether and 2.3 ml of dibenzylamine were added to the solution. The precipitating dibenzylamine salt was filtered off with suction, washed with ether and dried. 5.9 g of the dibenzylamine salt were obtained which melted between 160 and 165°C. For analysing the salt it was recrystallized from aqueous acetone and dried for 2 hours at 110°C.

Molecular formula: — $C_{32}H_{38}N_4O_8Cl_2$

40 Analysis: — Calculated: — C = 56.72% H = 5.65%

Found: — C = 56.29% H = 5.73%

Solubility in water: 0.08%

45 The dibenzylamine salt can also be usefully employed for working up saponification mixtures according to b) and for purification. To this end the oily acid is extracted with ether or dissolved and precipitated with dibenzylamine. After recrystallization the dibenzylamine salt can be easily decomposed by dissolving it in a little dimethyl formamide, adding dilute acid and extracting with an organic solvent.

e) The dibenzyl ethylene diamine salt.

50 5 g of the sodium salt obtained as described under c) were dissolved in 25 ml of water and 50 ml of ethanol as well as a solution of 2 g of dibenzylethylene diamine diacetate in 25 ml of water added. The precipitating crystallized dibenzyl ethylene-diamine salt was filtered off with suction, washed with water and dried. 5.5 g, melting between 195 and 199°C, were obtained. For analysis this was recrystallized from ethanol. M.p. = 198—201°C.

Molecular formula: — $C_{52}H_{88}O_{16}N_8Cl_4$
 Analysis: — Calculated: — C=52.04% H=5.54%
 Found: — C=51.40% H=5.66%
 Solubility in water: — 0.01%

5 In the same way as the dibenzylamine salt the dibenzyl ethylenediamine salt can 5
 also be used for isolation and purification.

f) The calcium salt.

10 In order to produce the calcium salt the acid was dissolved in aqueous alcohol 10
 and one equivalent of calcium acetate was added. By evaporating in vacuo a white
 powder was obtained to which acetone was added. After filtering off the undissolved
 substance the calcium salt was precipitated with ether. A white water-soluble powder
 melting between 173 and 176°C was obtained.

EXAMPLE 12: —

a) D-chloramphenicolcarbamidoisocaproic acid.

15 A solution of 16.3 g of chloramphenicol in a mixture of 8 ml of pyridine, 8.55 g 15
 of methyl-D-isocyanatoisocaproate and 100 ml of ethyl acetate was refluxed for 1
 hour and then evaporated in a vacuum until dry, the resultant oil being repeatedly
 digested with petroleum ether. After again evaporating in vacuo, 21.3 g of oil were
 20 obtained. After having been dissolved in 50 ml of ethanol it was saponified by 20
 the addition of 23 ml of a 2N-solution of sodium hydroxide. Having been allowed to stand
 at room temperature for 10 hours the mixture was diluted with water and the resultant
 cloudiness removed by shaking it out with ether. The acid in oil form was separated
 from the aqueous phase with dilute hydrochloric acid and extracted with ether. The
 ethereal phase was dried, treated with active carbon and evaporated until dry. 15.9 g of
 25 a vitrified acid were thus obtained. A sample crystallized slowly from aqueous ethanol, 25
 melting between 78 and 80°C.

Molecular formula: — $C_{18}H_{23}O_8N_3Cl_2$
 Analysis: — Calculated: — C=45.01% H=4.83%
 Found: — C=44.34% H=4.97%

30 b) The bibenzylamine salt. 30

This was prepared by the method described in Example 11 d). The salt melted
 between 189 and 191°C. For analysis the product was recrystallized from a mixture of
 dimethyl formamide and water and dried for 2 hours at 110°C.

35 Molecular formula: — $C_{32}H_{38}N_4O_8Cl_2$ 35
 Analysis: — Calculated: — C=56.72% H=5.65%
 Found: — C=56.75% H=5.81%
 Solubility in water: — 0.048%
 $[\alpha]_D^{20} = +21.7^\circ$ ($c=5$, in dimethyl formamide)

40 c) The dibenzyl ethylenediamine salt. 40

This salt was prepared in a manner analogous to that described in Example 11 e).
 For an analysis it was recrystallized from aqueous ethanol and dried for 2 hours at
 110°C. M.p. = 183—185°C.

45 Molecular formula: — $C_{52}H_{88}O_{16}N_8Cl_4$ 45
 Analysis: — Calculated: — C=52.04% H=5.54%
 Found: — C=51.97% H=5.62%
 Solubility in water: — 0.07%

EXAMPLE 13: —

a) D,L-chloramphenicolcarbamidoisocaproic acid.

50 This compound was obtained by the method according to Example 12 a), the iso- 50
 cyanatocarboxylic ester employed being the methyl-DL- α -isocyanatoisocaproate. The
 acid thus obtained was amorphous.

b) The dibenzylamine salt.

55 This salt was prepared by precipitating it from ethereal solutions of the acid. 55
 It can then be further purified. M.p. = 160 to 183°C. For an analysis the salt was
 reprecipitated from a mixture of dimethyl formamide and water.

Molecular formula: — $C_{22}H_{28}N_4O_8Cl_2$

Analysis: — Calculated: — C=56.72% H=5.65%

Found: — C=56.33% H=5.91%

Solubility in water: — 0.09%

$[\alpha]_D^{20} = +11.7^\circ$ ($c=5$, in dimethylformamide).

c) The sodium salt obtained from the carbamidoisocaproic acid as described in a) melted between 145 and 148°C.

EXAMPLE 14: —

Threo-1-*p*-dichloroacetamidophenyl-2-dichloroacetoamidopropan-1,3-diol-3-carbamido-acetic acid and its ethyl ester.

A suspension of 4.04 g of 1-*p*-dichloroacetamidophenyl-2-dichloroacetamidopropane-1,3-diol (prepared as described in U.S. Patent Specification No. 2,568,571) in 40 ml of ethyl acetate was refluxed with 1.29 g of ethylisocyanatoacetate and 2 ml of dry pyridine. Gradual dissolution was thus achieved. At the end of 30 minutes the mixture was cooled and petroleum ether added until the solution became cloudy. Rubbing and cooling caused the ester to crystallize. After filtration, washing with petroleum ether and drying, 4.6 g (86% of theory) of ester were obtained. For an analysis this was recrystallized from ethanol. Needles melting at 196 to 198°C were obtained.

Molecular formula: — $C_{18}H_{21}N_3O_7Cl_4$ Molecular weight: — 533.22

Analysis: — Calculated: — C=40.56% H=3.97% Cl=26.60%

Found: — C=40.29% H=4.05% Cl=25.95%

R_f -value (thin layer chromatography): — 0.79

[Adsorbent: — Silica gel (GF₂₅₄);

Solvent: — Butanol, saturated with 3% ammonia]

For saponification 2 g of the ester were dissolved in 10 ml of ethanol and 2 ml of a 2N-solution of sodium hydroxide added. After this solution had been allowed to stand at room temperature for 24 hours it was diluted with water and then shaken out three times with ethyl acetate to remove unsaponified residues. After acidification of the aqueous solution the acid was extracted with ethyl acetate. The ethyl acetate solution was then dried and evaporated, 1.2 g of an oily acid being obtained which crystallized from ethyl acetate with 1 mol of ethyl acetate. For analysis this was recrystallized twice from a little ethyl acetate.

Molecular formula: — $C_{16}H_{17}N_3O_7Cl_4 \cdot C_4H_8O_2$ Molecular weight: — 593.27

Analysis: — Calculated: — C=40.49% H=4.25%

Found: — C=40.64% H=4.30%

R_f -value (thin layer chromatography): — 0.22

[Adsorbent: — Silica gel (GF₂₅₄): —

Solvent: — Butanol, saturated with 3% ammonia]

For producing the sodium salt a solution of the acid in ethyl acetate was shaken out with a solution containing the calculated amount of sodium bicarbonate. The sodium salt was obtained in the form of a white water-soluble powder by evaporating the solution.

EXAMPLE 15: —

Threo-1-*p*-nitrophenyl-2-azidoacetylaminopropan-1,3-diol-3-carbamido-acetic acid and its ethyl ester.

A mixture of 10 g of D-(—)-threo-1-*p*-nitrophenyl-2-azidoacetylaminopropan-1,3-diol, 4.3 g of ethyl-isocyanatoacetate and 6.7 mls of pyridine were refluxed in 60 ml of ethyl acetate for 1 hour. The resultant clear solution was evaporated in vacuo until dry and the oily residue rubbed with ether, causing crystallization. After filtration, drying and recrystallization from dilute ethanol 11.8 g (82% of theory) of ester melting at 111 to 113°C were obtained.

Molecular formula: — $C_{16}H_{20}N_5O_8$ Molecular weight: — 424.39

Analysis: — Calculated: — C=45.28% H=4.75%

Found: — C=45.15% H=4.70%

[Adsorbent: — Silica gel (GF₂₅₄);

Solvent: — Butanol, saturated with 3% ammonia]

For saponification the ester was dissolved in ethanol, an equivalent amount of a 2N-solution of sodium hydroxide was added and the solution allowed to stand at room temperature for 14 hours. The yellow solution was then diluted with water, extracted with ethyl acetate to remove unsaponified residues and the aqueous solution acidified with dilute hydrochloric acid. The acid which separated in an oily form was extracted with ethyl acetate, the ethyl acetate solution being dried and decolourized with charcoal. The ethyl acetate solution was then extracted in portions with a solution of sodium bicarbonate until the pH was 7. The resultant solution was evaporated in vacuo until dry. By adding acetone to the residue, filtering off undissolved components, re-evaporating in vacuo and drying at 100°C the sodium salt was obtained in the form of a white powder. Chromatography proved this to be homogeneous.

R_f -value (thin layer chromatography): — 0.13

[Adsorbent: — Silica gel (GF₂₅₄);

Solvent: — Butanol, saturated with 3% ammonia]

EXAMPLE 16.

Threo-1-*p*-nitrophenyl-2-azidoacetylaminopropan-1,3-diol-3-carbamidoisocaproic acid and its methyl ester.

A mixture of 5.9 g of threo-1-*p*-nitrophenyl-2-azidoacetylaminopropan-1,3-diol, 3.4 g of the methylester of L-isocyanatoisocaproic acid and 4 ml of pyridine was refluxed for 1 hour. By evaporating the solution in vacuo the ester was obtained in the form of a difficultly crystallizing oil which was directly submitted to saponification. To this end 20 ml of ethanol and 10 ml of a 2N-solution of sodium hydroxide were added and the mixture was allowed to stand at room temperature for 5 hours. It was then diluted with water and extracted three times with ethyl acetate in order to remove impurities.

By acidification of the aqueous solution with dilute hydrochloric acid and extraction with ether an ethereal solution of the acid was obtained from which a crystallized salt was precipitated by the addition of 4 ml of dibenzylamine. After filtering with suction, washing with ether and drying, 7.5 g of the dibenzylamine salt were obtained which melted at 158 to 160°C after having been recrystallized from ethanol.

Molecular formula: — C₃₂H₃₉N₇O₈ Molecular weight: — 649.72

Analysis: — Calculated: — C = 59.16% H = 6.05%

Found: — C = 58.90% H = 6.13%

R_f -value (thin layer chromatography): — 0.25

[Adsorbent: — Silica gel (GF₂₅₄);

Solvent: — Butanol, saturated with 3% ammonia]

The dibenzylamine salt was decomposed by shaking a suspension in hydrochloric dilute ethanol and extracting with an organic solvent. The acid can be obtained from the organic phase in the form of its sodium salt by extraction with a solution of sodium bicarbonate and evaporating the aqueous solution.

EXAMPLE 17: —

Threo-1-*p*-nitrophenyl-2-phenylacetamido-propan-1,3-diol-3-carbamidoacetic acid and its ethyl ester.

a) Ethyl ester.

A mixture of 6.6 g (0.02 mol) D-threo-1-*p*-nitrophenyl-2-phenylacetamido-propan-1,3-diol [produced from D-threo-1-*p*-nitrophenyl-2-amino-propan-1,3-diol and phenylacetyl chloride, having M.p. 110°C and $[\alpha]_D^{20} = +4.8^\circ$ (c = 1, in ethanol)], 40 ml ethyl acetate, 4 ml pyridine and 2.4 ml ethyl isocyanatoacetate was heated to boiling under reflux for 1 hour. By evaporation an oil was obtained which solidified on rubbing with ether. After recrystallization from ethanol/water 6.4 g (70% of theory) of the ester (M.p. 132°—133°C) was obtained. For example this was recrystallized twice more from ethanol/water. M.p. 134°C.

Molecular formula: — C₂₂H₂₅N₃O₈

Analysis: — Calculated: — C = 57.51% H = 5.48%

Found: — C = 57.59% H = 5.65%

$[\alpha]_D^{20} = +18.7^\circ$ (c = 1, in ethanol)

b) Sodium salt

The ester was saponified in aqueous alcoholic solution with 2N-sodium hydroxide.

The usual working-up gave an oily acid, which was converted in known manner to the sodium salt. A white powder chromatographically pure was obtained.

R_f -value (thin-layer chromatography): — 0.20

[Adsorbent: — silica gel (GF₂₅₄)]

Solvent: — Butanol saturated with 3% ammonia]

$[\alpha]_D^{20} = +18.1^\circ$ ($c = 1$, in water).

EXAMPLE 18: —

Threo-1-*p*-nitrophenyl-2-phenoxyacetamido-propan-1,3-diol-3-carbamido-acetic acid and its ethyl ester.

6.92 g of D-threo-1-*p*-nitrophenyl-2-phenoxyacetamido-propan-1,3-diol [obtained by acylating D-threo-1-*p*-nitrophenyl-2-amino-propan-1,3-diol with phenoxyacetyl chloride in acetone/water in the presence of sodium carbonate, having an M.p. = 132—133°C (crystallized from ethanol/water).

Molecular formula: — C₁₇H₁₈N₂O₆

Analysis: — Calculated: — C = 58.95% H = 5.24%

Found: — C = 58.80% H = 5.31%

$[\alpha]_D^{20} = -48.1^\circ$ ($c = 1$ in ethanol) in admixture with 40 ml ethylacetate, 4 ml pyridine, 2.4 ml ethyl isocyanatoacetate was heating to boiling under reflux for 30 minutes. After drying in vacuo a non-crystalline oil was obtained, which was dissolved in 20 ml ethanol and saponified by admixture with 10 mls of 2N-sodium hydroxide. After standing for an hour at about 40°C, it was diluted with water, extracted twice with ethyl acetate and the acid precipitated from the aqueous phase with dilute hydrochloric acid. After extraction with ethyl acetate, drying and evaporation 5.5 g of an oily residue was obtained and was crystallized from ethanol/water. M.p. = 140—142°C.

Molecular formula: — C₂₀H₂₁N₃O₈

Analysis: — Calculated: — C = 53.69% H = 4.73%

Found: — C = 53.52% H = 4.91%

$[\alpha]_D^{20} = -3.19^\circ$ ($c = 1$ in ethanol).

EXAMPLE 19: —

Threo-1-*p*-nitrophenyl-2-benzamido-propan-1,3-diol-3-carbamido- α -blutaric acid and its dimethyl ester.

a) Dimethyl ester.

A mixture of 6.3 g of D-threo-1-*p*-nitrophenyl-2-benzamido-propan-1,3-diol [produced from D-threo-1-*p*-nitrophenyl-2-amino-propan-1,3-diol and benzyl chloride in acetone/water in the presence of sodium carbonate, and having a M.p. = 172°C

$[\alpha]_D^{20} = -121.5^\circ$ ($c = 1$, in ethanol).

Molecular formula: — C₁₈H₁₈N₂O₅

Analysis: — Calculated: — C = 60.75% H = 5.10%

Found: — C = 60.47% H = 5.18%

with 40 mls ethyl acetate, 4 ml pyridine, and 4 g dimethyl L- α -isocyanato-glutarate was heated to boiling under reflux for 30 minutes. It was then evaporated to dryness and the residue crystallized from ethanol/water. 4.7 g of the ester, M.p. 161—163°C, were obtained. For analysis it was twice recrystallized from ethanol. M.p. 165°C.

Molecular formula: — C₂₄H₂₇N₃O₁₀

Analysis: — Calculated: — C = 55.70% H = 5.26%

Found: — C = 56.02% H = 5.37%

$[\alpha]_D^{20} = -56.5^\circ$ ($c = 1$, in dimethylformamide)

b) Sodium salt.

By saponifying the ester with 2N-sodium hydroxide there is produced the corresponding sodium salt, which is obtained as a white, chromatographically pure powder.

R_f -value (thin layer chromatography): — 0.68

[Adsorbent: — silica gel (GF₂₄₅)]

Solvent: — glacial acetic acid: butanol: water = 60:20:20]

$[\alpha]_D^{20} = -39.9^\circ$ ($c = 1$, in water).

EXAMPLE 20: —

Threo-1-*p*-nitrophenyl-2-benzamido-propan-1,3-diol-3-carbamido acetic acid and its ethyl ester.

a) Ethyl ester.

A mixture of 6.3 g D-threo-1-*p*-nitrophenyl-2-benzamido-propan-1,3-diol (Example 19), 40 ml ethyl acetate, 4 ml pyridine and 2.4 ml ethyl isocyanatoacetate was

heated to boiling under reflux for 30 minutes. After evacuation in vacuo an oil was produced, which solidified (yield 6.9 gms) on rubbing with ether. After recrystallization from ethanol/water the M.p. was 161°—162°C.

Molecular formula:— $C_{21}H_{23}N_3O_8$

Analysis:— Calculated:— C=56.63% H=5.20%

Found:— C=56.45% H=5.30%

$[\alpha]_D^{20} = +46.6^\circ$ (c=1, in ethanol).

b) Sodium salt.

a white, chromatographically pure powder

R_f -value (thin layer chromatography):— 0.70

[Adsorbent:— silica gel (GF₂₄₅)

Solvent:— glacial acetic acid: butanol: water = 60:20:20]

$[\alpha]_D^{20} = +46.5^\circ$ (c=1, in water)

EXAMPLE 21:—

Threo-1-*p*-nitrophenyl-2-isobutyramido-propan-1,3-diol-3-carbamidoacetic acid and its ethyl ester.

a) Ethyl ester.

A mixture of 2 g D-threo-1-*p*-nitrophenyl-2-isobutyramido-propan-1,3-diol [prepared from D-threo-1-*p*-nitrophenyl-2-amino-propan-1,3-diol and isobutyryl chloride in ethyl acetate/water in the presence of sodium carbonate. M.p. = 138°C.

Molecular formula:— $C_{13}H_{18}N_2O_8$

Analysis:— Calculated:— C=55.31% H=6.43%

Found:— C=55.17% H=6.54%

$[\alpha]_D^{20} = +23.2^\circ$ (c=1, in ethanol)], with 20 ml ethyl acetate, 14 ml pyridine and 0.92 g ethyl isocyanatoacetate was heated to boiling under reflux for 40 minutes and evaporated to dryness, and the residue was recrystallized from ethanol/water. 2.1 g of the ester was produced. M.p. 137°C.

Molecular formula:— $C_{18}H_{25}N_3O_8$

Analysis:— Calculated:— C=52.55% H=6.12%

Found:— C=52.54% H=6.20%

$[\alpha]_D^{20} = +34.2^\circ$ (C=1, in ethanol)

b) Sodium salt.

a white, chromatographically pure powder.

R_f -value (thin layer chromatography):— 0.15

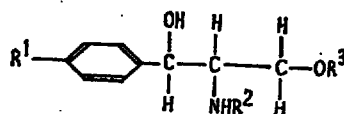
[Adsorbent: silica gel (GF₂₅₄)

Solvent: butanol saturated with 3% ammonia]

$[\alpha]_D^{20} = -18.5^\circ$ (c=0.6, in water).

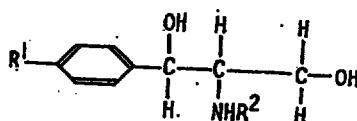
WHAT WE CLAIM IS:—

1. A process of producing D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives of the general formula I:



(I)

wherein R^1 is hydrogen, an NO_2 —, CN —, CH_3SO_2 —, CH_3S —, NH_2 — or XCONH —group or a halogen atom, X being the dichloromethyl azidomethyl, benzyl, phenoxyethyl, phenyl or isopropyl radical, R^2 is Cl_2CHCO — or $\text{N}_3\text{CH}_2\text{CO}$ or other XCO —group, wherein X has the above stated meaning and R^3 represents a carbamido-carboxylic acid ester radical, which comprises reacting compounds of the general formula II:



(II)

heated to boiling under reflux for 30 minutes. After evacuation in vacuo an oil was produced, which solidified (yield 6.9 gms) on rubbing with ether. After recrystallization from ethanol/water the M.p. was 161°—162°C.

Molecular formula: — $C_{21}H_{23}N_3O_8$

Analysis: — Calculated: — C=56.63% H=5.20%

Found: — C=56.45% H=5.30%

$[\alpha]_D^{20} = +46.6^\circ$ (c=1, in ethanol).

b) Sodium salt.

a white, chromatographically pure powder

R_f -value (thin layer chromatography): — 0.70

[Adsorbent: — silica gel (GF₂₄₅)

Solvent: — glacial acetic acid: butanol: water = 60:20:20]

$[\alpha]_D^{20} = +46.5^\circ$ (c=1, in water)

EXAMPLE 21: —

Threo-1-*p*-nitrophenyl-2-isobutyramido-propan-1,3-diol-3-carbamidoacetic acid and its ethyl ester.

a) Ethyl ester.

A mixture of 2 g D-threo-1-*p*-nitrophenyl-2-isobutyramido-propan-1,3-diol [prepared from D-threo-1-*p*-nitrophenyl-2-amino-propan-1,3-diol and isobutyryl chloride in ethyl acetate/water in the presence of sodium carbonate. M.p. = 138°C.

Molecular formula: — $C_{13}H_{18}N_2O_5$

Analysis: — Calculated: — C=55.31% H=6.43%

Found: — C=55.17% H=6.54%

$[\alpha]_D^{20} = +23.2^\circ$ (c=1, in ethanol)], with 20 ml ethyl acetate, 14 ml pyridine and 0.92 g ethyl isocyanatoacetate was heated to boiling under reflux for 40 minutes and evaporated to dryness, and the residue was recrystallized from ethanol/water. 2.1 g of the ester was produced. M.p. 137°C.

Molecular formula: — $C_{13}H_{18}N_2O_5$

Analysis: — Calculated: — C=52.55% H=6.12%

Found: — C=52.54% H=6.20%

$[\alpha]_D^{20} = +34.2^\circ$ (C=1, in ethanol)

b) Sodium salt.

a white, chromatographically pure powder.

R_f -value (thin layer chromatography): — 0.15

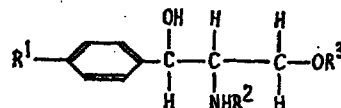
[Adsorbent: silica gel (GF₂₅₄)

Solvent: butanol saturated with 3% ammonia]

$[\alpha]_D^{20} = -18.5^\circ$ (c=0.6, in water).

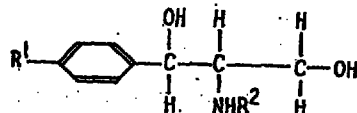
WHAT WE CLAIM IS: —

1. A process of producing D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives of the general formula I:



(I)

wherein R^1 is hydrogen, an NO_2 —, CN —, CH_3SO_2 —, CH_3S —, NH_2 — or XCONH —group or a halogen atom, X being the dichloromethyl azidomethyl, benzyl, phenoxyethyl, phenyl or isopropyl radical, R^2 is Cl_2CHCO — or $\text{N}_3\text{CH}_2\text{CO}$ — or other XCO —group, wherein X has the above stated meaning and R^3 represents a carbamido-carboxylic acid ester radical, which comprises reacting compounds of the general formula II:



(II)



wherein R¹ and R² have the same meaning as above, with esters of isocyanatocarboxylic acids.

2. A process as claimed in claim 1, in which the reactant of general formula II is chloramphenicol.

3. A process as claimed in claim 1, in which the reactant of general formula II is D(-)-threo-1-*p*-nitrophenyl-2-azidoacetylaminopropan-1,3-diol.

4. A process as claimed in claim 1, in which the reactant of formula II is the 4'-methyl-sulphonyl analogue of chloramphenicol.

5. A process as claimed in any of claims 1 to 4, in which the compound of general formula II is reacted with the ester of an isocyanatocarboxylic acid in the presence of a tertiary base.

6. A process as claimed in any of claims 1 to 5 followed by saponification of the resulting D-threo-1-phenyl-2-amino-1,3-propane diol-carbamidocarboxylic acid ester to yield the corresponding carbamidocarboxylic acid.

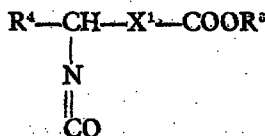
7. A process as claimed in claim 6, in which the resultant D-threo-1-phenyl-2-amino-1,3-propanediol-carbamidocarboxylic acid ester product is saponified to the corresponding carbamidocarboxylic acid with the aid of an alkali metal or alkaline earth metal hydroxide or carbonate or an amine or hydroxyalkyl amine.

8. A process as claimed in claim 6 or 7 followed by conversion of the carbamidocarboxylic acid to a salt thereof by reaction with an organic or inorganic base.

9. A process as claimed in claim 8, in which the acid is salified with dibenzyl amine or a derivative of ethylenediamine including dibenzylethylene diamine.

10. A process as claimed in any of claims 1 to 9, in which the ester of an isocyanato-carboxylic acid employed is the α -isocyanatocarboxylate ester.

11. A process as claimed in any of claims 1 to 9, in which the ester of the isocyanatocarboxylic acid employed has the general formula



wherein R⁴ is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms, an alkyl radical having an interposed hetero-atom and containing up to 6 carbon atoms, a carboalkoxy or carboalkoxyalkyl radical or an aryl radical, R² is a alkyl radical having up to 4 carbon atoms and X¹ represents a direct C—C bond or the grouping $-(\text{CH}_2)_n-$, *n* being an integer between 1 and 6.

12. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is an alkyl- α -isocyanatoacetate.

13. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is an alkyl-L- α -isocyanatoisocaproate.

14. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is an alkyl- α -isocyanato- γ -methylmercaptobutyrate.

15. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is an alkyl- α -isocyanatoisovalerate.

16. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is an alkyl- α -isocyanatopropionate.

17. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is methyl- α -isocyanato(phenyl) acetate.

18. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is dimethyl- α -isocyanatoglutarate.

19. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is dimethyl- α -isocyanatosuccinate.

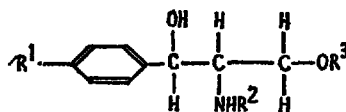
20. A process as claimed in claim 11, in which the ester of the isocyanatocarboxylic acid is methyl- ϵ -isocyanatocaproate.

21. A process of producing novel D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives of the general formula I substantially as hereinbefore described and exemplified.

22. D-threo-1-phenyl 1-2-amino-propane-1,3-diol derivatives when produced by a process claimed in any of claims 1 to 21.

23. D-threo-1-Phenyl-2-amino-propan-1,3-diol derivatives having the general formula



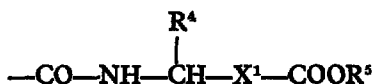


wherein R¹ is H or a —NO₂, —CN, CH₃SO₂—, CH₃S—, NH₂— or XCONH—radical or a halogen atom, X being the dichloromethyl, azidomethyl, benzyl, phenoxymethyl, phenyl or isopropyl radical, R² is an XCO—radical in which X has the above meaning, and R³ is a carbamidocarboxylic acid or carbamidocarboxylic acid ester radical, and the salts of the carbamidocarboxylic acids with organic or inorganic bases.

24. D-threo-1-phenyl-2-amino-propan-1,3-diol derivatives claimed in claim 23, wherein R¹ is H or Cl or a —NO₂, —CN, CH₃SO₂, CH₃S—, NH₂— or —NHCOX radical, X having the same meaning as in claim 23.

25. D-threo-1-Phenyl-2-amino-propan-1,3-diol derivatives claimed in claim 23 or 24, wherein R² is the Cl₂CHCO— or N₃CH₂CO—radical.

26. D-threo-1-Phenyl-2-amino-propan-1,3-diol derivatives claimed in claim 23, 24 or 25, wherein R³ is a radical of the formula



in which formula R⁴ is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms, an alkyl radical having an interposed hetero-atom and containing up to 6 carbon atoms, a carbalkoxy or carbalkoxyalkyl radical or an aryl radical, R⁵ is hydrogen or n alkyl radical having up to 4 carbon atoms and X¹ is a direct C—C bond or a (CH₂)_n group wherein n is an integer from 1 to 6.

27. Chloramphenicol carbamidoacetic acid and its ethyl ester.

28. L-Chloramphenicol carbamidoisocaproic acid and its methyl ester.

29. D°Chloramphenicol carbamidoisocaproic acid.

30. Alkali metal and alkaline earth metal salts of the acids claimed in any of claims 23 to 28.

31. Sodium salt of chloramphenicol carbamidoacetic acid.

32. Dibenzylamine and dibenzylethylene diamine salts of the acids claimed in any of claims 23 to 28.

33. D - threo - 1 - p - Nitrophenyl - 2 - azidoacetyl amino - propane - 1,3 - diol - 3-carbamidoacetic acid, and its ethyl ester.

34. D - threo - 1 - p - Nitrophenyl - 2 - azidoacetyl amino - propane - 1,3 - diol - 3-carbamidoisocaproic acid and its methyl ester.

35. D - threo - 1 - p - Dichloroacetamidophenyl - 2 - dichloroacetamido - propane-1,3-diol-3-carbamido-acetic acid and its ethyl ester.

36. D - threo - 1 - p - Nitrophenyl - 2 - phenylacetamido - propan - 1,3 - diol - 3-carbamido - acetic acid and its ethyl ester.

37. D - threo - 1 - p - Nitrophenyl - 2 - phenoxyacetamido - propan - 1,3 - diol - 3-carbamido - acetic acid and its ethyl ester.

38. D - threo - 1 - p - Nitrophenyl - 2 - benzamido - propan - 1,3 - diol - 3-carbamido-α- glutaric acid and its dimethyl ester.

39. D - threo - 1 - p - Nitrophenyl - 2 - benzamido - propan - 1,3 - diol - 3-carbamido-acetic acid and its ethyl ester.

40. D - threo - 1 - p - Nitrophenyl - 2 - isobutyramido - propan - 1,3 - diol - 3-carbamido-acetic acid and its ethyl ester.

41. Therapeutic compositions containing a compound claimed in any of claims 22 to 40 in admixture with a pharmaceutical carrier.

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