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PATENT SPECIFICATION

NO DRAWINGS

1.188.159



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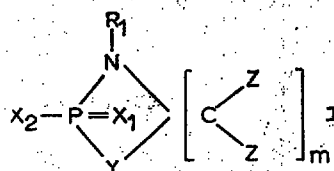
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COMPLETE SPECIFICATION

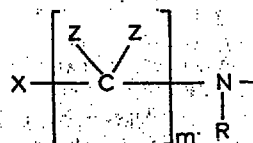
Process for the production of New N-Substituted Amides and Esteramides of Phosphoric and Thiophosphoric Acid

We, ASTA-WERKE AKTIENGESELLSCHAFT CHEMISCHE FABRIK, a body corporate organised under the laws of Germany, of 79—91 Bielefelder Strasse, Brackwede/Westfalen, Germany, 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 is related to new cyclic phosphoric and thiophosphoric acid derivatives of Formula I



wherein R_1 is a lower alkyl group having from 1 to 4 carbon atoms being substituted with one or several halogen atoms, X_1 is oxygen or sulphur, Y is oxygen, —NH— or —NZ₁—, Z_1 being a lower alkyl group having from 1 to 4 carbon atoms, optionally substituted with one or several halogen atoms or hydroxy groups, Z is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms, a halogen atom, the hydroxy group or the hydroxy methyl group, m is 2 or 3 and X_2 is the ethylene imino group or the group having the formula

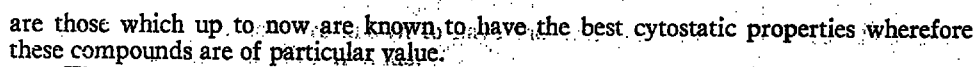
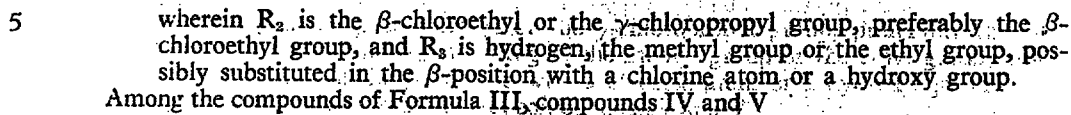
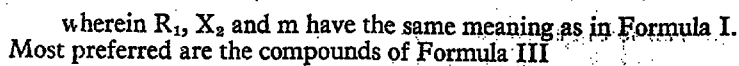


wherein R is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms, optionally substituted with one or several halogen atoms or one or several hydroxy groups, X is a halogen atom or the hydroxy group and Z and m have the above given meanings.

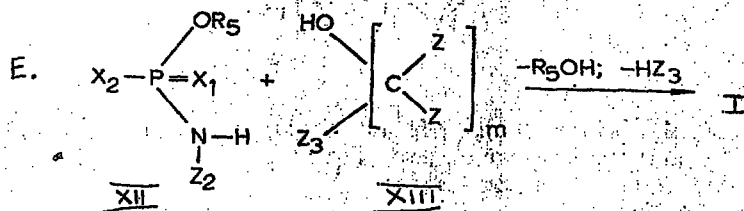
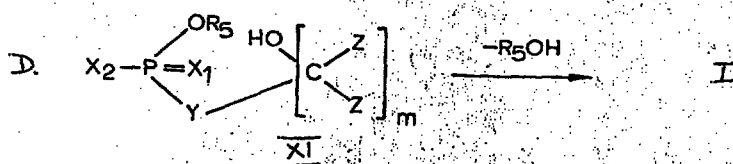
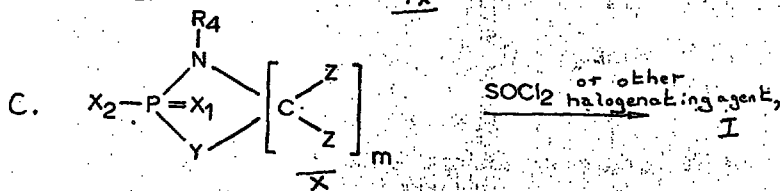
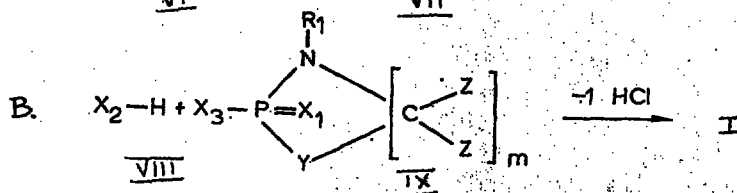
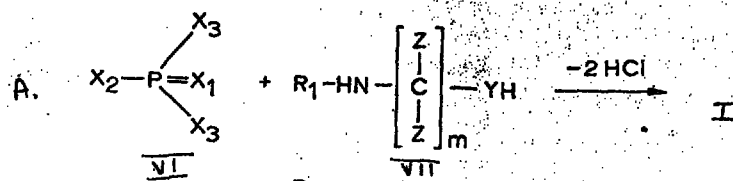
The present invention also provides pharmaceutical preparations comprising compounds of formula I and a pharmaceutically acceptable carrier.

Because of their particularly valuable properties, those compounds of the above Formula I are preferred wherein X_1 represents oxygen. Among these compounds, those compounds are preferred which correspond to Formula II

[Price 5s. 0d.]



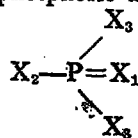
The new compounds of Formula I may be produced by one of the following methods designated by A, B, C, D and E:



In the above Formulae VI to XIII, R₁, X₁, X₂, Y, Z, and m have the same meaning as in Formula I; additionally, X₃ is a halogen atom, preferably a chlorine atom, and R₁ is a lower alkyl group having from 1 to 4 carbon atoms and being substituted with one or several hydroxy groups, R₅ is alkyl, aralkyl or aryl, preferably aryl such as phenyl, Z₂ is hydrogen or Z₁, and Z₃ is a halogen. The synthesis according to method A is carried out, for instance, in accordance with the German patent specifications 1,057,119 or 1,054,997 describing the reaction of phosphoric acid amide dichlorides of Formula VI in an inert solvent in the presence of two mol equivalents of triethylamine as acid binding agent. The synthesis according to method B is carried out as described for instance in J. org. Chem. 26, (1961) page 4743. The method C applies usual methods for exchanging aliphatic hydroxy groups to halogen atoms. The method D is carried out by heating the starting product to an elevated temperature, as is described for instance in Belgian patent specification 554,888. The method E applies usual procedures for alkylating amides in combination with the conditions of method D. The starting materials VI, VII, VIII, IX, X, XI, XII, and XIII used in the above methods may be obtained as described in the literature.

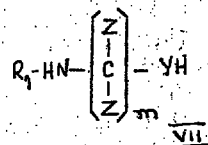
Thus, the process according to the present invention for producing the new cyclic phosphoric and thiophosphoric acid derivatives of Formula I is characterized in that

A) a phosphoric acid or thiophosphoric acid amide dihalogenide of Formula VI



VI

wherein X_3 is halogen, preferably chlorine, and X_1 and X_2 have the same meaning as in the above Formula I, is subjected to reaction with a compound of the Formula VII

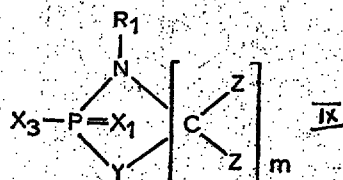


- 5 wherein R_1 , Y , Z and m have the same meaning as in Formula I,
or
B) a compound of Formula VIII

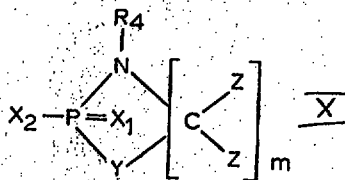


VIII

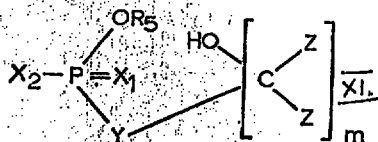
- 10 wherein X_2 has the same meaning as in the above Formula I, is subjected to reaction with a cyclic phosphoric or thiophosphoric acid amide halogenide of Formula IX



- 15 wherein X_3 is a halogen atom, preferably a chlorine atom, and X_1 , R_1 , Y , Z and m have the same meaning as in the above Formula I, in the presence of an acid binding agent or
C) a compound of Formula X



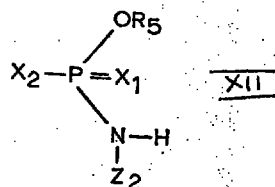
- 20 wherein R_4 is a lower alkyl group having from 1 to 4 carbon atoms and being substituted with one or several hydroxy groups and X_1 , X_2 , Y , Z and m have the same meaning as in the above Formula I, is subjected to reaction with a halogenating agent or
D) a compound of Formula XI



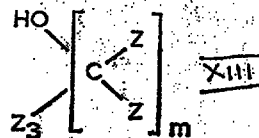
wherein R_5 is an alkyl, aralkyl or an aryl group, particularly an aryl group and most preferred a phenyl group, and X_1 , X_2 , Y , Z and m have the same meaning as in the above Formula I,

is heated at an elevated temperature, preferably in the range of about 100°C. to about 250°C. or

E) a compound of Formula XII



wherein Z_2 is hydrogen or Z_1 , R_5 has the same meaning as in the above Formula XI and X_1 , X_2 and Z_1 have the same meaning as in the above Formula I, is subjected to reaction with a compound of Formula XIII



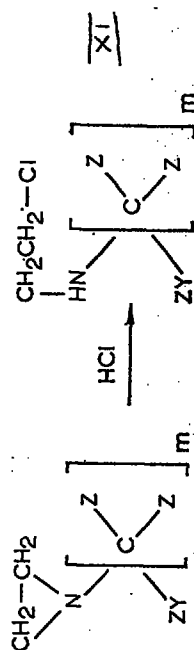
wherein Z_3 is halogen, preferably chlorine, and Z and m have the same meaning as in the above Formula I,

in the presence of an acid binding agent at an elevated temperature, preferably in the range of about 100°C. to about 250°C.

Preferably, the reactions A, B, and C are carried out in an inert organic solvent such as a halogenated lower aliphatic hydrocarbon such as chloroform or methylene dichloride, or in an aromatic hydrocarbon such as benzene or toluene, or in an ether such as diethyl ether or dioxane. The acid binding agent should preferably be present in an amount corresponding to at least two mol equivalents in the method embodiment A, and in an amount corresponding to at least one mol equivalent in the method embodiment B in order to preferably absorb the total amount of acid HX_3 produced during the reactions. Many basic compounds are known to be useful as acid binding agents, such as alkali metal carbonates and bicarbonates and particularly tertiary amines such as triethyl amine or pyridine. The reactions A, B, and C may be carried out at room temperature or at an elevated temperature such as a temperature elevated to the boiling point of the solvent used. Halogenating agents for exchanging aliphatically bound hydroxy groups to halogen atoms are known to the expert, too. Such agents are for instance the phosphorus trihalogenides such as phosphorus trichloride PCl_3 and phosphorus tribromide PBr_3 , the phosphoric acid halogenides such as phosphorus pentachloride PCl_5 , phosphorus oxychloride POCl_3 and phosphorus oxybromide, the halogenides of sulphurous and sulphuric acid such as sulphuryl chloride SO_2Cl_2 and thionyl chloride SOCl_2 , or phosgene. Thionyl chloride is preferably used for exchanging hydroxy groups to chlorine atoms as this agent may be most simply handled. Groups in the compounds which may be attacked by the halogenating agent should possibly be protected by known protective groups which subsequently are split off again, as is known to the expert. On the other hand, it may be desired to exchange hydroxy groups in compounds of Formula X, wherein both R_4 as well as X_2 may contain hydroxy groups, to halogen atoms at the same time.

The starting component VII may be an ethylene imino alkanol of Formula XI,

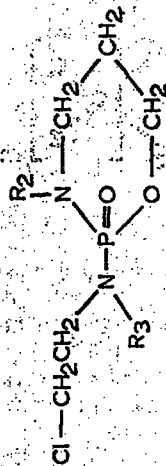
too:



In this case, XI is split up *in situ* by the hydrochloric acid produced during the reaction, thus yielding VII ($R_1 = -CH_2CH_2Cl$) which subsequently undergoes reaction with VI according to the method embodiment A to yield I.

The products according to the present invention of Formula I are useful in human and veterinary medicine as cytostatically active compounds. Test results of pharmacological tests with products according to the present invention are given in the following Table I.

TABLE I	
10	Curative and lethal doses of various cyclic phosphoric acid amide esters of the 10 Formula



upon intraperitoneal application.

Compound according to Example	R ₃	R ₂	LD 50 (1)		CD 50 (4)		Therapeutic Index
			mg./ kg.	mmol./ kg.	mg./ kg.	mmol./ kg.	
							LD 50 (1)
A	—CH ₂ CH ₂ Cl	—H	160	0.57	12	0.04	13
1	—CH ₂ CH ₂ Cl	—CH ₂ CH ₂ Cl	75	0.23	8	0.025	9
4	—H	—CH ₂ CH ₂ Cl	160	0.61	12	0.046	13

Test compound A = N,N-bis(β -chloroethyl)-amino-N',O'-propylene-phosphoric acid ester diamide.

Determination of CD 50 (4) with a Yoshida-Ascites-Sarcoma of rats with a total dose D subdivided into 4 subsequent days. Start up of therapy at the day of sarcoma implantation; Test period: 90 days.

Determination of LD 50 (1) with a single administration to rats of the same race; Test period: 14 days.

The compound according to Example 1 is characterized by a very good chemotherapeutic effectiveness to the mouse tumours Sarcoma 37 and Ehrlich-Carcinoma known to be resistant to chemotherapy; the known comparative test compound A is not effective or exerts effectiveness only with subtoxic doses. The compound of Example 4 is characterized over the known test compound in that the accumulation of the toxic effectiveness is similar in the lethality test. Thus, the LD 50 (4) of compound A is 140 mg./kg. and thus lower than the LD 50 (1) while the LD 50 (4) of the compound according to Example 4 amounts to 190 mg./kg. and thus is significantly higher than the LD 50 (1). This lower toxic accumulation is of importance in the treatment over prolonged periods of time.

Furthermore, the compound of Formula V is characterized by a high solubility in water and furthermore represents a new type of cytostatic wherein the 2-chloroethyl groups are not bound to one and the same nitrogen atom as in the nitrogen mustard compound; on the contrary, the two 2-chloroethyl groups are substituted at two different amide nitrogen atoms.

Finally, in comparison to the known cytostatic N,N-bis- β -chloroethylamino-N',O-propylene-phosphoric acid ester diamide (test compound A) which is well accepted in the medical art under the generic name Cyclophosphamide, the compounds of the present invention are characterized by an improved stability in aqueous solutions as follows from Table II. When allowing compounds of the present invention to stand in a bicarbonate buffer solution (pH 7.5) for 10 days at 37.5°C., chlorine ions are split off in an amount of only about 1/6 of the amount split off with the known test compound A.

TABLE II

Compound of Example No.	equiv./mol. of chloride ions split off after 10 days
A	1.26
1	0.12
4	0.18

The following Examples serve to further illustrate the present invention without however limiting the same thereto.

EXAMPLE 1

N,N,N'-Tris-(2-chloroethyl)-N',O-propylene phosphoric acid ester diamide
259 g. (1 mol of N,N-bis-(2-chloroethyl) phosphoric acid amide dichloride, 209 g. (1.2 mol) of N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride (crude), 1000 cc. of methylene dichloride and 344 g. (3.4 mol) of triethylamine.

N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride is dissolved in the methylene dichloride. N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride is suspended in this solution and triethylamine is added thereto dropwise with stirring. The temperature of the solution rises to boiling. After the termination of the addition, the mixture is heated to boiling for another 6 hours. Thereafter, the reaction mixture is cooled down and allowed to stand overnight at about 0°C. The precipitated triethylamine hydrochloride is filtered off with suction. The resulting solution is evaporated, the residue (about 370 g.) is triturated with about 3.2 l. of ether and is heated to boiling for a short period of time. The ethereal solution is decanted from the insolubles (about 90 g.). The solution is rendered to pH 6.5 to 7 by the addition of ethereal hydrochloric acid and then is filtered over charcoal and thereafter is evaporated. During evaporation, the temperature should not rise above 40°C. The residue is dissolved in ether and in an amount corresponding to half of its weight (240 g. of residue dissolved in 120 cc. of ether), the ethereal solution is cooled to -5°C. and is inoculated.

5 After standing for 25 hours, 140 g. have been separated by crystallization. After separation by filtration with suction, the mother liquor is diluted with ether to 5 times its volume, the solution is filtered over charcoal, is again evaporated and the residue is again dissolved in a volume corresponding to half of the weight of the residue. Another cooling to -5°C . and inoculation produces further 18 g. of the desired compound. Total yield: 161 g. (50% of the theoretical).
Fp.: 50 to 51°C .

EXAMPLE 2

10 N,N,N'-Tris-(2-chloroethyl)-N',O-propylene phosphoric acid ester diamide
64.7 g. (0.25 mol) of N,N-bis-(2-chloroethyl) phosphoric acid amide dichloride, 130 cc. of dioxane, 25.2 g. (0.25 mol) of ethylene imino propanol, 25.2 g. (0.25 mol) of triethylamine and 50 cc. of dioxane.

15 The solution of ethylene imino propanol and triethylamine in 50 cc. of dioxane is added dropwise with stirring to the solution of N,N-bis-(2-chloroethyl) phosphoric acid dichloride in 130 cc. of dioxane. The temperature is kept at 50°C . with cooling during the addition. After termination of the addition, the reaction mixture is stirred at 50°C . for another three hours. Thereafter, the mixture is cooled and precipitated triethylamine hydrochloride is separated by filtration with suction. The mother liquor is evaporated in a vacuum and the residue is dissolved in 500 cc. of ether. This solution is washed 3 times with water, then washed with dilute soda lye and finally washed another time with water. Thereafter, it is dried over anhydrous sodium sulphate and evaporated in a vacuum to about 130 g. This solution is cooled down to -5°C . and inoculated, thus causing crystallization and separation of 28 g. of the desired product. After separation thereof, the mother liquor is diluted with ether to about five times the initial volume. It is then filtered over charcoal and evaporated. The residue is dissolved in such a volume of ether which corresponds to half of the weight of the residue. The solution is again cooled down to -5°C . Upon inoculation, another 10 g. of the desired compound crystallizes. Total yield: 38 g. (47% of the theoretical).
Fp.: 50 to 51°C .

EXAMPLE 3

30 N,N,N'-Tris-(2-chloroethyl)-N',O-propylene phosphoric acid ester diamide

42.6 g. of (0.30 mol) of N,N-bis-(2-chloroethyl)-amine, 150 cc. of methylene dichloride, 32.7 g. (0.15 mol) of N-chloroethyl-N,N-propylene phosphoric acid ester amide monochloride and 65 cc. of methylene dichloride.

35 42.6 g. of N,N-bis-(2-chloroethyl)-amine are dissolved in 150 cc. of methylene dichloride. A solution of 32.7 g. of N-(2-chloroethyl)-N,O-propylene phosphoric acid ester amide monochloride in 65 cc. of methylene dichloride are added thereto with stirring. The mixture is heated to boiling for 1 hour and thereafter evaporated in a vacuum. The residue is triturated with 350 cc. of anhydrous ether and precipitated N,N-bis-(2-chloroethyl)-amine hydrochloride is separated by filtration with suction. The ethereal solution is washed with dilute hydrochloric acid and, thereafter, with a solution of sodium bicarbonate. After drying over anhydrous sodium sulfate, the ether is distilled off and the oily residue is carefully dried, dissolved in ten times its volume of anhydrous ether, filtered over activated charcoal and evaporated again. The residue is dissolved in 40 cc. of anhydrous ether. After cooling at -5°C ., crystallization is initiated by inoculation. After standing for 24 hours, the precipitated crystals are filtered off with suction and dried in a vacuum. Yield: 24.3 g. (50.1% of the theoretical).
Fp.: 51 to 52°C .

EXAMPLE 4

50 N,N'-Bis-(2-chloroethyl)-N',O-propylene phosphoric acid ester diamide

127.6 g. (1.1 mol) of N-(2-chloroethyl)-amine hydrochloride are suspended in a solution of 218 g. (1 mol) of N-(2-chloroethyl)-N,O-propylene phosphoric acid ester amide monochloride in 600 cc. of methylene dichloride, and 212 g. of triethylamine are added thereto dropwise with stirring. The reaction mixture is heated to boiling by the reaction heat. After termination of the addition, the reaction mixture is heated to boiling for another 2 hours. Thereafter, it is cooled to room temperature and the precipitated triethylamine hydrochloride is separated by filtration with suction. The filtrate is extracted with about 60 cc. of dilute hydrochloric acid (pH 3), then twice with about 60 cc. of water, thereafter with about 60 cc. of dilute soda lye and finally twice with about 60 cc. of water. After drying over anhydrous sodium sulfate, methylene dichloride is distilled off under normal pressure. The oily residue is dried in a vacuum and

thereafter extracted in a perforator with 500 cc. of anhydrous ether. The oily extract crystallizes upon inoculation and standing in an ice box. After standing for several hours, the precipitate is filtered off, washed with a small amount of cold ether and dried in a vacuum at room temperature. Yield: 185 g. (71% of the theoretical). Fp.: 39 to 41°C.

EXAMPLE 5

N-Methyl-N,N'-bis-(2-chloroethyl)-N',O-propylene phosphoric acid ester diamide.
90.8 g. of triethylamine are added to a suspension of 52.2 g. of 2-chloroethyl-3-hydroxypropyl-amine hydrochloride in 210 cc. of methylene dichloride. A solution of 52.5 g. of N-methyl-N-(2-chloroethyl)-phosphoric acid amide dichloride in 52.5 cc. of methylene dichloride is added thereto with stirring. During the addition, the reaction mixture is heated to boiling by the reaction heat. After termination of the addition, the reaction mixture is heated to boiling for another 5 hours. After cooling to room temperature, the precipitated triethylamine hydrochloride is filtered off with suction. The filtrate is washed subsequently with dilute hydrochloric acid, water, 2 N-soda lye and then twice with water. After drying over anhydrous sodium sulfate, the solution is evaporated in a vacuum and the oily residue is dissolved in twelve times its volume of ether. The resulting solution is filtered over activated charcoal and is again evaporated. The colourless oil is dried in a vacuum. Yield: 52 g. (75.5% of the theoretical).

EXAMPLE 6

N,N-Ethylene-N',O-propylene phosphoric acid ester diamide
A solution of 0.73 g. of ethylene imine and 11.1 g. of triethylamine in 30 cc. of ether are added with stirring to a solution of 21.8 g. of N-(2-chloroethyl)-N,O-propylene phosphoric acid ester amide monochloride in 132 cc. of anhydrous ether. The temperature of the reaction mixture rises and triethylamine hydrochloride is precipitated. After termination of the addition, the reaction mixture is stirred at room temperature for another 2 hours. Thereafter, precipitated triethylamine hydrochloride is filtered off with suction, the filtrate is filtered over activated charcoal and the solvent is distilled off. The oily residue is carefully dried in a vacuum and is then dissolved in ten times its volume of anhydrous ether. The solution is filtered over activated charcoal once more and is again evaporated. The oily residue is carefully dried in a vacuum. Yield: 15 g. (67% of the theoretical).

EXAMPLE 7

N,N-Bis-(2-chloroethyl)-N'-(3-chloropropyl)-N',O-propylene phosphoric acid ester diamide
31.9 g. (1/10 mol) of N,N-bis-(2-chloroethyl)-N'-(3-hydroxypropyl)-N',O-propylene phosphoric acid ester diamide are dissolved in 80 cc. of chloroform and a solution of 14 cc. (2/10 mol) of thionylchloride in 20 cc. of chloroform are added thereto with stirring. There occurs a weakly exothermic reaction. After termination of the addition, nitrogen is bubbled through the reaction mixture while heating the mixture to a temperature of 38 to 40°C. Formation of HCl and SO₂ is terminated after 3 hours. After cooling to room temperature, the solution is shaken with 0.1 N hydrochloric acid until a remaining acid reaction of the mixture is obtained. Thereafter, the mixture is neutralized by washing with dilute sodium bicarbonate solution and the neutralized chloroform solution is dried over anhydrous sodium sulfate. After separation of sodium sulfate, chloroform is distilled off in a vacuum and the oily residue is carefully dried. Yield: 16 g. (47.4% of the theoretical).

EXAMPLE 8

N,N-Bis-(2-chloroethyl)-N'-(3-chloropropyl)-N',O-propylene phosphoric acid ester diamide
25.9 g. of N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride (0.1 mol), 18.8 g. of N-(3-chloropropyl)-N-(3-hydroxypropyl)-amine hydrochloride (0.1 mol), 30.3 g. triethylamine (0.3 mol), and 100 cc. of dioxane.
The above starting materials are heated at 50°C. with stirring for 3 hours. After cooling to room temperature, the precipitated triethylamine hydrochloride is filtered off with suction and the solution is evaporated in a vacuum. The oily residue is dissolved in 250 cc. of ether and the solution is shaken with 0.1 N hydrochloric acid until the solution remains acid. Thereafter, the solution is neutralized by washing with a dilute sodium bicarbonate solution and the neutralized mixture is dried over anhydrous sodium sulfate. After separation of the sodium sulfate, the ether is cautiously distilled off and the oily residue is carefully dried. Yield: 25 g. (74% of the theoretical).

EXAMPLE 9

N,N'-Bis-(2-chloroethyl)-N-(2-hydroxyethyl)-N',O-propylene phosphoric acid ester diamide

A solution of 10.9 g. of N-(2-chloroethyl)-N,O-propylene phosphoric acid ester amide monochloride in 50 cc. of chloroform is added dropwise to a solution of 8.0 g. of N-(2-chloroethyl)-N-(2-hydroxyethyl)-amine hydrochloride (1/20 mol) and 10.1 g. of triethylamine (1/10 mol) in 50 cc. of chloroform at 28°C. within a period of 45 minutes. Stirring is continued for another 2 hours at room temperature and thereafter for another two hours at 40°C. After standing over night, the precipitated triethylamine hydrochloride is filtered off with suction and the solution is evaporated in a vacuum. The oily residue is extracted in a soxhlet for several hours with anhydrous ether and the ethereal extract is evaporated in a vacuum. The resulting oily product is once more extracted with anhydrous ether in an apparatus for extracting liquids and the resulting solution is again evaporated in a vacuum. The resulting oily product is mixed with a small amount of aluminium oxide and is distilled over a porcelain frit G4. A weakly yellow oil of medium viscosity and soluble in water is obtained which oil is dried in a high vacuum for several hours. Yield: 6.5 g. (42.5% of the theoretical).

EXAMPLE 10

Solutions in solubilizer useful for the production of injection solutions

- 20 a) N,N,N' - Tris - (2 - chloroethyl) - N',O - propylene phosphoric acid ester di-
amide 200 mg.,
solubilizer 1-methyl-3-(2-hydroxyethyl)-imidazolidone-(2) ad 2cc.
For producing injection solutions, the above solution is diluted with 8 to 10 cc. of
water;
25 b) N,N'-Bis-(2-chloroethyl)-N',O-propylene phosphoric acid ester diamide 500 mg.,
solubilizer 1-methyl-3-(2-hydroxyethyl)-imidazolidone-(2) ad 2.5 cc.
For producing injection solutions, the above solution is diluted with about 15 to 20
cc. of water.

EXAMPLE 11

- 30 Dragées
a) N,N,N'-Tris-(2-chloroethyl)-N',O-propylene phosphoric acid ester di-
amide 50 mg.
Calcium phosphoric. DAB 6 anhydr 110 mg.
35 Amylum maidis 65 mg.
Aerosol comp. 3 mg.
Magnesium stearicum 2 mg.

The above components are intimately mixed and pressed to biconvex dragée cores having a diameter of 8 mm. and a radius of crown of 6 mm. The thus obtained dragée cores are covered with a sugar coating in manners known *per se* to yield dragées of a total weight of 400 mg. It is preferable to protect the dragée core with an insulating coating consisting of a polyacrylic acid product and talcum.

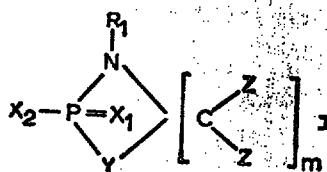
- 40 b) N,N'-Bis-(2-chloroethyl)-N',O-propylene phosphoric acid ester di-
amide 50.0 mg.
45 Calcium phosphoric DAB 6 anhydr 61.5 mg.
Amylum maidis 50.0 mg.
Aerosol comp. 50.0 mg.
Polyvinylpyrrolidonum 7.0 mg.
Magnesium stearicum 1.5 mg.

50 The thus obtained biconvex dragée cores having a diameter of 8 mm. and a radius of crown of 6 mm. are coated with a sugar coating in manners known *per se* to yield dragées having a total weight of 390 mg. It is again preferable to protect the core by an insulating coating consisting of a polyacrylic acid product and talcum.

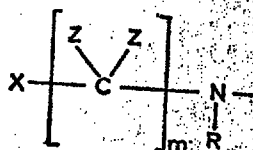
The sugar coatings may be colored by the addition of dyestuffs allowed under the respective Common Market Regulations.

55 WHAT WE CLAIM IS:—

1. Process for the production of new cyclic phosphoric and thiophosphoric acid derivatives of the Formula I

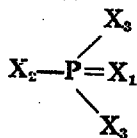


- 5 wherein R_1 is a lower alkyl group having from 1 to 4 carbon atoms being substituted with one or several halogen atoms, X_1 is oxygen or sulphur, Y is oxygen, $-NH-$ or $-NZ_1-$, Z_1 being a lower alkyl group having from 1 to 4 carbon atoms, optionally substituted with one or several halogen atoms or one or several hydroxy groups, Z is hydrogen, a lower alkyl group having from 1 to 4 carbon atoms, a halogen atom, the hydroxy group or the hydroxymethyl group, m is 2 or 3, and X_2 is the ethylene imino group or the group having the formula

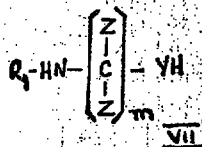


- 10 wherein R is hydrogen or a lower alkyl group having from 1 to 4 carbon atoms optionally substituted with one or several halogen atoms or one or several hydroxy groups, X is a halogen atom or the hydroxy group and Z and m have the above given meaning,

- 15 comprising
A) subjecting a phosphoric acid or thiophosphoric acid amide dihalogenide of Formula VI



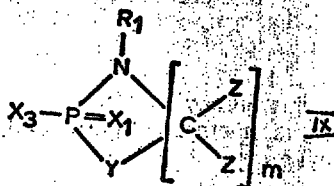
- 20 wherein X_3 is halogen and X_1 and X_2 have the same meaning as in the above Formula I,
to reaction with a compound of the Formula VII



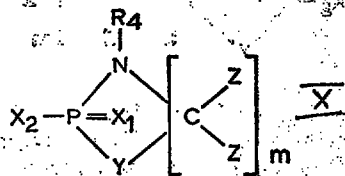
- 25 wherein R_1 , Y , Z and m have the same meaning as in Formula I,
or
B) subjecting a compound of Formula VIII



- wherein X_2 has the same meaning as in the above Formula I,
to reaction with a cyclic phosphoric or thiophosphoric acid amide halogenide of the Formula IX

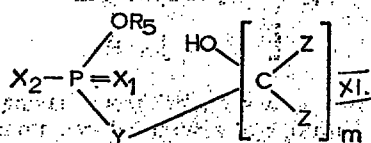


wherein X_3 is a halogen atom and X_1 , R_1 , Y , Z and m have the same meaning as in the above Formula I,
 C) subjecting a compound of Formula X



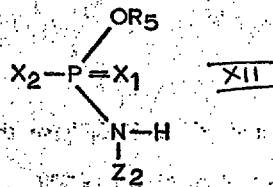
wherein R_4 is a lower alkyl group having from 1 to 4 carbon atoms and being substituted with one or several hydroxy groups and X , X_2 , Y and Z and m have the same meaning as in the above Formula I,
 to reaction with a halogenating agent

or
 D) heating a compound of Formula XI

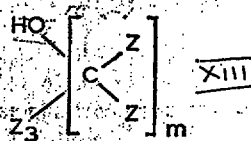


wherein R_5 is an alkyl, aralkyl or an aryl group and X_1 , X_2 , Y , Z and m have the same meaning as in the above Formula I,
 at an elevated temperature

or
 E) subjecting a compound of Formula XII



wherein Z_2 is hydrogen or Z_1 , R_5 has the same meaning as in the above Formula XI and X_1 , X_2 and Z have the same meaning as in the above Formula I,
 to reaction with a compound of Formula XIII



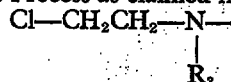
wherein Z_3 is halogen and Z and m have the same meaning as in the above Formula I,
 in the presence of an acid binding agent at an elevated temperature.

2. Process as claimed in claim 1, wherein reactions A, B and C are carried out in an inert organic solvent.

3. Process as claimed in claims 1 or 2, wherein X_1 is oxygen.

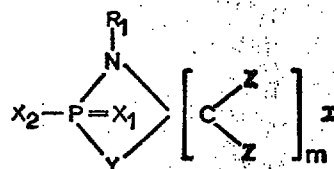
4. Process as claimed in claim 3, wherein Y is oxygen and Z is hydrogen.

5. Process as claimed in claim 4, wherein X_2 is the group

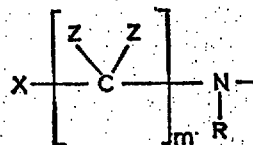


R_3 is the β -chloroethyl or γ -chloropropyl group,
 m is 3 and R_3 is hydrogen, the methyl group, the ethyl group, the β -chloroethyl group or the β -hydroxy ethyl group.

6. Process according to claim 5, wherein R_1 is the β -chloroethyl group.
7. Process according to claim 6, wherein R_2 is the β -chloroethyl group.
8. Process according to claim 6, wherein R_3 is hydrogen.
9. A process as claimed in claim 1 substantially as described herein.
10. The products of formula I whenever produced by a process as claimed in any of the preceding claims.
11. The products of formula I whenever produced as described in the preceding Examples 1 to 9.
12. Pharmaceutical preparations comprising compounds of formula I and pharmaceutically acceptable carrier.
13. Pharmaceutical preparations whenever produced as described in the preceding Examples 10 and 11.
14. A compound of the formula



wherein R_1 represents an alkyl group with 1 to 4 carbon atoms substituted by one or more halogen atoms, X_1 represents an oxygen or sulphur atom, Y represents an oxygen atom or a group of the formula $-NH-$ or $-NZ_1-$ in which Z_1 represents an alkyl group with 1 to 4 carbon atoms optionally substituted by one or more halogen atoms or hydroxy groups, each Z represents hydrogen, halogen, an alkyl group with 1 to 4 carbon atoms, a hydroxy group or a hydroxymethyl group, m represents 2 or 3 and X_2 represents an ethyleneimino group or a group of the formula



wherein R represents hydrogen or an alkyl group with 1 to 4 carbon atoms optionally substituted by one or more halogen atoms or hydroxy groups, X represents a halogen atom or hydroxy group and Z and m have the meanings given above.

15. N,N,N' -tris-(2-chloroethyl)- N',O -propylene phosphoric acid ester diamide.
16. N,N' -bis-(2-chloroethyl)- N',O -propylene phosphoric acid ester diamide.
17. N -methyl- N,N' -bis-(2-chloroethyl)- N',O -propylene phosphoric acid ester diamide.
18. N,N -ethylene- N' -(2-chloroethyl)- N',O -propylene phosphoric acid ester diamide.
19. N,N -bis-(2-chloroethyl)- N' -(3-chloropropyl)- N',O -propylene phosphoric acid ester diamide.
20. N,N' -bis-(2-chloroethyl)- N -(2-hydroxyethyl)- N',O -propylene phosphoric acid ester diamide.

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