

PATENT SPECIFICATION

(11) 1341 170

1341 170

NO. DRAWINGS

(21) Application No. 7881/72 (22) Filed 21 Feb. 1972

(31) Convention Application No. P 21 07 936.7

(32) Filed 19 Feb. 1971

(31) Convention Application No. P 22 01 675.7

(32) Filed 14 Jan. 1972 in

(33) Germany (DT)

(44) Complete Specification published 19 Dec. 1973

(51) International Classification C07F 9/22 A61K 27/00

(52) Index at acceptance

C2P 1L1 2E11A 2E18B 2E19D 2E24 2E25B 2L11A 2L18B
2L19F 2L25B 2L30C 6 7

(72) Inventors HERBERT ARNOLD
FRIEDRICH BOURSEAUX
JURGEN POTEL and
NORBERT BROCK

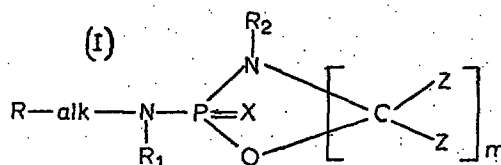


(54) ALKYL SULFONIC ACID ESTERS OF 1,3,2-OXAZAPHOSPHACYCLIC COMPOUNDS

(71) We, ASTA-WERKE AKTIENGESellschaft CHEMISCHE
FABRIK, a body corporate organised under the laws of Germany of 4812 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:—

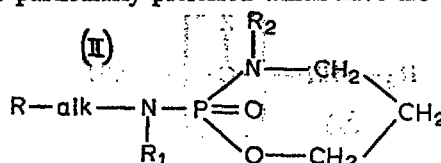
The present invention relates to alkyl sulfonic acid esters of 1,3,2-oxazaphospha-
cyclic compounds which produce a high immunosuppressing activity. The invention
further relates to a process for the production thereof and to pharmaceutical prepara-
tions containing the same.

The new compounds according to the present invention correspond to the
formula I.



wherein R is a halogen atom, preferably a chlorine atom, or an alkylsulfonyl group
having a straight or branched alkyl chain with 1 to 6 carbon atoms, R₁ and R₂ are
each hydrogen or an alkyl group with 1 to 4 carbon atoms which alkyl group may be
substituted with a halogen atom, preferably a chlorine atom, or with an alkylsulfonyl
group having a straight or branched alkyl chain with 1 to 6 carbon atoms, R₁ and R₂
being identical or different from each other; there being present in the molecule of
formula I at least one alkylsulfonyl group, and alk represents a straight or branched
alkylene group with 2 or 3 carbon atoms in a chain intervening between the group R
and the N atom and, if branched, with a total of 3 or 4 carbon atoms, X represents
oxygen or sulphur, each Z independently represents a hydrogen atom or an alkyl group
having from 1 to 4 carbon atoms and m is 2 or 3.

Because of their favourable compatibility those compounds of formula I are
preferred, wherein X is oxygen. Because of their high immunosuppressing activity,
those compounds are particularly preferred which have the formula II

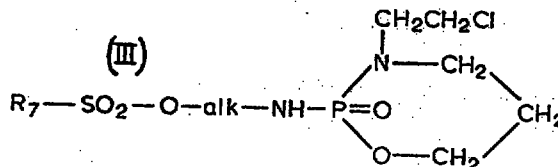


[Price 25p]

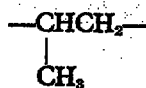
Price 75p

wherein R , R_1 , R_2 and alk have the same meaning as in formula I.

Among these compounds of formula II the compounds of formula III



are particularly preferred, wherein R_7 is an unsubstituted alkyl group having from 1 to 6 carbon atoms in a straight or branched chain and alk is the group $-\text{CH}_2\text{CH}_2-$,



or



in particular the group $-\text{CH}_2\text{CH}_2-$. Among this group of compounds those compounds show a particularly high immunosuppressing activity and therefore are most preferred wherein alk is $-\text{CH}_2\text{CH}_2-$ and R_7 is the methyl or ethyl group or alk is

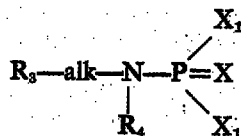


and R_7 is the methyl group.

It is surprising that the compounds of formula I show a strong immunosuppressive activity which has not been known heretofore with alkyl sulfonic acid esters. The compounds of the following Examples 1, 19, 25, 27, 28 and 30 in particular produce a substantial or even complete suppression of antibody formation until the 7th day after the administration of the antigen. The immunoactivity in connection with the Brucella immunisation of rats is used to demonstrate this activity.

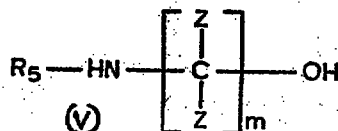
The new compounds of formula I are produced by using methods known as such. The processes for the production of the compounds according to the present invention comprise either:

A) subjecting a compound of formula IV



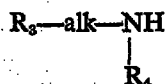
IV

wherein R_3 has the same meaning as R in formula I or is a hydroxy group, R_4 has the same meaning as R_1 in formula I or is an alkyl group having from 1 to 4 carbon atoms and being substituted by a hydroxy group, alk and X have the same meaning as in formula I and X_1 is a halogen atom, preferably a chlorine atom, to reaction with a compound of formula V



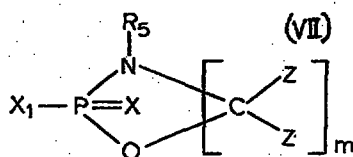
wherein R_5 has the same meaning as R_4 in formula IV and Z and m have the same meaning as in formula I, or

B) subjecting a compound of the general formula VI



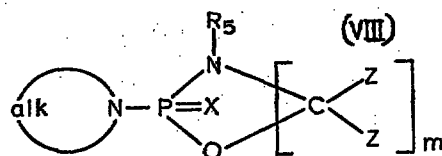
VI

wherein R_3 and R_4 have the same meaning as in formula IV and alk has the same meaning as in formula I, to reaction with a compound of formula VII



wherein X_1 has the same meaning as in formula IV, R_5 has the same meaning as in formula V and X, Z and m have the same meaning as in formula I, or

C) subjecting a compound of formula VIII

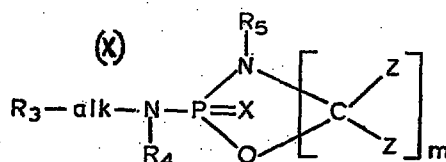


wherein R_5 has the same meaning as in formula V and X, Z, alk and m have the same meaning as in formula I, to reaction with a compound of formula IX



IX

wherein R_6 has the same meaning as in formula IV, and converting the hydroxy groups in the resulting compounds of formula X



whenever one or more of the R_3 , R_4 and R_5 groups represent or carry a hydroxy group, into halogen atom(s) or group(s) $-\text{OSO}_2R_6$, R_6 being a straight or branched alkyl group having from 1 to 6 carbon atoms, for example by subjecting said hydroxy compounds to reaction with a halogenating agent or a sulfonic acid halogenide $R_6\text{SO}_2\text{Hal}$, R_6 having the same meaning as above and Hal being a halogen atom, preferably a chlorine atom, and, if desired, replacing one or more of any halogen atoms in the resulting compounds of formula X, wherein none of the R_3 , R_4 and R_5 groups represent or carry a hydroxy group but one or several of the R_3 , R_4 and R_5 groups represent or carry a halogen atom, by the group $-\text{OSO}_2R_6$ by subjecting such a compound of formula X to reaction with a compound of formula XI



XI

wherein R_6 has the above given meaning and Me is a metal of the first or second main or sub-group of the periodic system of elements, and preferably is silver.

The reactions are preferably carried out in the presence of an inert solvent such

as acetonitrile or a lower halogenated hydrocarbon such as chloroform or methylene chloride, or in an ether such as diethyl ether or dioxane, or in an aromatic hydrocarbon such as benzene or toluene. The reactions are carried out at a temperature ranging from room temperature to the boiling point of the reaction mixture.

The reactions are preferably carried out in the presence of an acid binding agent. The acid binding agent should be present in an amount ranging from 1 to 2 mole equivalents. There are numerous known alkaline compounds which may be used as acid binding agents such as alkali metal and alkaline earth metal carbonates and bicarbonates and particularly tertiary amines such as triethylamine and pyridine.

Halogenating agents for replacing aliphatically bound hydroxy groups by halogen atoms are also known. Useful for this purpose are for instance the phosphorus halides such as phosphorus trichloride or tribromide, phosphorus pentachloride, phosphorus oxychloride or oxybromide, the sulfurous and sulfonic acid halides such as sulfur chloride and thionyl chloride, or phosgene. Thionylchloride is most preferably used in view of the ease with which it may be handled.

The usual carriers employed for pharmaceutical preparations, are used, in this case in conjunction with a compound according to formula I as the active agent, these being pharmacologically inert products which are well known for the production of tablets, dragees, suppositories and injection solutions.

The following Examples further illustrate the present invention without however limiting the same thereto. The compounds according to the present invention are characterized by their infrared spectra and show characteristic

$\text{P}=\text{O}-$ bands at 1188 to 1275 cm^{-1} ,
 $-\text{C}-\text{SO}_2-\text{C}-$ bands at 1330 to 1376, 1165 to 1175, 905 to 975 and 787 to 805 cm^{-1} ,
 $-\text{P}-\text{O}-\text{C}-$ bands at about 1050 and 975 cm^{-1} and
 $\text{NH}-$ bands at 3200 to 3300 cm^{-1} .

Example 1

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 113.2 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 360 cc. of anhydrous dioxane are added dropwise at 15–18°C. to a solution of 31.6 g. of ethanolamine and 57 g. of triethylamine in 300 cc. of anhydrous dioxane. Stirring is continued for one hour at 30–35°C. Thereafter, the precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is washed 3 to 4 times with each 100 cc. of ether. After drying in a high vacuum, the resulting 2-(2-hydroxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a faintly yellow oil.

Yield: 121.3 g. (97% of the theoretical).

A solution of 121.3 g. (0.5 mole) of the above compound and 50.6 g. (0.5 mole) of triethylamine in 320 cc. of dioxane is prepared. This solution is added to a solution of 57.3 g. (0.5 mole) of methanesulfonic acid chloride in 340 cc. of dioxane dropwise within 30 minutes at 26–28°C. Thereafter, 150 cc. of ether are added and stirring at 10°C. is continued for another 30 minutes. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated at 30–35°C. in a water jet vacuum. Ether is added to the oily residue which crystallizes while standing in an ice box after seeding. The product is purified by dissolving it in ethanol and adding ether to the ethanolic solution and allowing to stand in the ice box. The product is obtained in nice colored crystals upon extraction in a soxhlet apparatus with a mixture of methylene chloride and ether.

Yield: 111 g. (69% of the theoretical)

M.p.: 81–82°C.

Example 2

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

8.9 g. of 2-chloroethylamine hydrochloride are suspended in a solution of 15.3 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 150 cc. of methylene chloride. 14.9 g. of triethylamine are added thereto with stirring. The mixture is heated to boiling for additional two hours and the precipitated triethylamine

hydrochloride is filtered off with suction. The filtrate is washed consecutively with dilute hydrochloric acid, water, and 10% aqueous soda solution. After drying and evaporation of the solvent, the residue is evaporated under normal pressure and the residue is extracted in perforator by means of anhydrous ether. The resulting 2-(2-chloroethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide crystallizes in the ice-box upon seeding.

Yield: 13.05 g. (71% of the theoretical)

M.p.: 39—41°C.

A mixture of 13.05 g. (1/20 mole) of the above compound and 10.15 g. (1/20 mole) of silver methanesulfonate in 80 cc. of acetonitrile is heated to boiling for 8 hours. After cooling, the precipitated silver chloride is filtered off with suction. The acetonitrile is distilled off at room temperature in a water jet vacuum. The oily residue is extracted several times with ether and thereafter dissolved in chloroform. The solvent is again distilled off and the product evaporated finally in a high vacuum.

Yield in raw material: 11.3 g. (70% of the theoretical).

The purification is effected chromatographically by means of silica gel. The absorbed material is eluted by means of a mixture of 2 parts of benzene, 1 part of chloroform and 1 part of methanol. The isolated product is recrystallized from ether.

M.p.: 80—82°C.

Example 3

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 9.6 g. (1/10 mole) of methanesulfonic acid in 45 cc. of anhydrous ether is added dropwise to a solution of 22.4 g. (1/10 mole) of 2-(ethyleneimino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 95 cc. of anhydrous ether within 20 minutes at 25°C. The mixture separates into two layers. The ethereal layer is decanted off and the oily phase is dissolved in 50 cc. of isopropanol. The solution is diluted with 50 cc. of ether. The resulting product crystallizes upon standing in the ice box and seeding.

Yield: 14.7 g. (46% of the theoretical)

M.p.: 80—82°C.

Example 4

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 10.9 g. (1/20 mole) of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide and 10.1 g. (1/10 mole) of triethylamine in 50 cc. of chloroform are added dropwise at room temperature to a solution of 11 g. (1/20 mole) of 2-mesyloxyethylamine hydrochloride in 50 cc. of chloroform.

The mixture is stirred at room temperature for 2 hours and thereafter for another 2 hours at 40°C. After standing for 20 hours, the solvent is distilled off in a water jet vacuum. Acetone is added to the residue and the mixture is cooled. The insoluble triethylammonium halogenide mixture is filtered off with suction. Thereafter, the acetone is evaporated and ether is added to the oily residue. The mixture is heated to boiling and acetone is added in such an amount to just yield a clear solution. The desired product crystallizes upon cooling.

Yield: 5.5 g. (34% of the theoretical)

F.: 80—82°C.

Example 5

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 6.6 g. of N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride and 11.6 g. of triethylamine in 150 cc. of methylene chloride is added to a solution of 9.8 g. of N-(2-mesyloxyethyl)-phosphoric acid amide dichloride in 50 cc. of methylene chloride dropwise at 25°C. with stirring and cooling for some time. The mixture is stirred at room temperature for an additional hour and for further 2 hours at 40°C. The solvent then is distilled off in a water jet vacuum and triethylamine hydrochloride is precipitated by the addition of dioxane. The precipitate is filtered off. The filtrate is evaporated, finally in a high vacuum.

The resulting product is purified as described in Example 2.

M.p.: 80—82°C.

Example 6

2-[N-(2-Mesyloxyethyl)-ethylamino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

5 A solution of 19.5 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 75 cc. of anhydrous dioxane is added to a solution of 7.9 g. of N-ethyl-ethanolamine and 9.4 g. of triethylamine in 75 cc. of anhydrous dioxane dropwise with stirring at 45°C. The reaction mixture is stirred at 45°C. for additional 4 hours and thereafter for 20 hours at room temperature. The precipitated triethylamine hydrochloride is filtered off and the filtrate is evaporated in a water jet vacuum. The residue is washed several times with ether. 1-[N-(2-Hydroxyethyl)-ethylamino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a yellow oil of medium viscosity. 10

Yield: 21.7 g. (89.5% of the theoretical).

15 A solution of 9.2 g. of methanesulfonyl chloride is added to a solution of 21.7 g. of the above compound and 8.4 g. of triethylamine in 150 cc. of anhydrous dioxane dropwise within 10 minutes with stirring at 30°C. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The resulting oil is washed with petrol ether for 1 hour in a perforator and thereafter is extracted with ether for 2 hours. Upon evaporation of the ether an oil is obtained which is purified chromatographically as described in Example 2. 20

Yield: 6 g.
 n_D^{21} : 1.4950.

Example 7

2-(2-Mesyloxyethylamino)-3-(2-mesyloxyethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

25 20.3 g. (1/10 mole) of silver methanesulfonate are suspended in a solution of 13.05 g. (1/20 mole) of 2-(2-chloroethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide (prepared as described in Example 2) in 200 cc. of acetonitrile. The mixture is heated for about 50 hours consecutively to a temperature starting with 20°C. until reaching 100°C. with the exclusion of air moisture and light and with thorough stirring. The amount of separated silver chloride is 12.4 g. (86% of the theoretical). 30

35 The solvent is evaporated at 40°C. in a water jet vacuum and the residue is extracted five times with anhydrous ether. The residue is dissolved in anhydrous methylene chloride and the solution is allowed to stand in the ice-box for 20 hours. Precipitated crystalline silver methanesulfonate is filtered off and the filtrate is again evaporated. Three times the oily residue is dissolved in methylene chloride, filtered over activated charcoal evaporating thereafter the solvent.

40 Upon drying in a high vacuum a highly viscous yellow oil is obtained.
Yield: 7.4 g. (39% of the theoretical)
 n_D^{22} : 1.4955. 40

Example 8

2-(2-Chloroethylamino)-3-(3-mesyloxypropyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

45 A solution of 39.2 g. of N-(2-chloroethyl)-phosphoric acid amide dichloride in 160 cc. of anhydrous dioxane is added to a solution of 26.7 g. of dipropanolamine and 42 g. of triethylamine in 120 cc. of anhydrous dioxane dropwise at room temperature within an hour. Stirring is continued for further 2 hours and the precipitated triethylamine hydrochloride is filtered off with suction. The filtrate is evaporated in a water jet vacuum and the residue is dissolved in chloroform. The solution is neutralized with ethereal hydrochloric acid, the solution thereafter is dried and the solvent is again evaporated. 2-(2-Chloroethylamino)-3-(3-hydroxypropyl)-tetrahydro-2H-1,2,3-oxazaphosphorine-2-oxide is obtained as a yellow-brown oil. 50

Yield: 14.4 g. (28% of the theoretical).

55 A solution of 14.4 g. of the above compound and 5.7 g. of triethylamine in 110 cc. of anhydrous dioxane is added to a solution of 6.45 g. of methanesulfonyl chloride in 65 cc. of anhydrous dioxane dropwise with stirring at a temperature of 30°C. within 30 minutes. The separated triethylamine hydrochloride is filtered off and the filtrate is evaporated in a vacuum. The residue is dissolved in a mixture of 1 part of isopropanol and 1 part of ether. The solution is allowed to stand for 2 hours in an ice-bath with scratching at intervals. The separated crystals are filtered off with suction and 60

are washed in a mixture of isopropanol and ether and thereafter with ether alone. The product is purified by extraction with ether in a soxhlet apparatus.

Yield: 6.5 g. (34.6% of the theoretical)

M.p. 72°C.

5

Example 9

5

2-(2-Mesyloxyethylamino)-3-(3-chloropropyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

10

A solution of 17.6 g. of 2-chloro-3-(3-chloropropyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 55 cc. of anhydrous dioxane is added to a solution of 4.6 g. of ethanolamine and 7.6 g. of triethylamine in 55 cc. of anhydrous dioxane dropwise within an hour at a temperature ranging from 15—18°C. The reaction product is stirred for another hour at room temperature. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is washed with ether several times and dried in a high vacuum. 2-(2-Hydroxyethylamino)-3-(3-chloropropyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a yellowish oil.

10

15

15

Yield: 17 g. (84.8 of the theoretical).

20

A solution of 17 g. of the above compound and 6.7 g. of triethylamine in 60 cc. of dioxane is added to a solution of 7.6 g. of methanesulfonyl chloride in 50 cc. of dioxane dropwise with stirring within about 20 minutes at a temperature ranging from 26—28°C. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum.

20

25

The reaction product is purified chromatographically over silica gel by means of a mixture of benzene-chloroform-methanol. The resulting oil crystallizes upon cooling and the product is recrystallized twice from isopropanol. The product is obtained as snow-white crystals.

25

Yield: 7.9 g. (35.5% of the theoretical)

M.p.: 92—93°C.

30

Example 10

30

2-[(2-Mesyloxyethyl)-(2-chloroethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

35

A solution of 38.6 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 150 cc. of chloroform is added to a solution of 28.3 g. of N-(2-chloroethyl)-N-(2-hydroxyethylamine)hydrochloride and 35.5 g. of triethylamine in 150 cc. of chloroform dropwise with stirring at 28°C. within an hour. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated. The residue is extracted with anhydrous ether in a perforator. The ether is evaporated from the resulting solution. The resulting 2-[(2-chloroethyl)-(2-hydroxyethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a faintly yellow oil.

35

40

40

Yield: 23 g. (42.5% of the theoretical).

45

A solution of 23 g. of the above product and 7.6 g. of triethylamine in 200 cc. of anhydrous ether is added to a solution of 8.65 g. of methanesulfonyl chloride in 200 cc. of anhydrous ether dropwise with stirring at 25°C. within 20 minutes. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The resulting yellow oil is extracted with ether in a perforator. The ether is evaporated from the resulting solution and the residue is dissolved in chloroform, washed consecutively with chilled dilute aqueous ammonia and thereafter with water. The solution then is dried over anhydrous sodium sulfate and is again evaporated. The resulting faintly yellow oil is purified chromatographically over silica gel as described in Example 2. The resulting product is a colorless oil.

45

50

50

Yield: 10.5 g.

n_D^{25} : 1.0526.

55

Example 11

55

2-(3-Mesyloxypropylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

60

A solution of 37.4 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 140 cc. of anhydrous dioxane is added dropwise to a solution of 12.95 g. of propanolamine-1,3 and 17.3 g. of triethylamine in 140 cc. of anhydrous dioxane dropwise with stirring within 50 minutes at a temperature ranging from

60

15—18°C. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is washed several times with ether. Upon drying in a high vacuum, the resulting 2-(3-hydroxypropyl-amino) - 3 - (2 - chloroethyl) - tetrahydro - 2H - 1,3,2 - oxazaphosphorine - 2 - oxide is obtained as a highly viscous clear oil.

Yield: 38.6 g. (86% of the theoretical).

A solution of 38.6 g. of the above compound and 15.5 g. of triethylamine in 120 cc. of anhydrous dioxane is added to a solution of 17.2 g. of methanesulfonyl chloride in 120 cc. of anhydrous dioxane dropwise with stirring within 30 minutes at a temperature ranging from 28—30°C. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The oily residue is dissolved in water and purified by means of the ion exchanger Duolite (A 102). Anhydrous ether is added to the colorless oil and the mixture is cooled in an ice-bath and scratched from time to time. Thus, the product crystallizes. The crystals are recrystallized from ethyl acetate.

Yield: 13.9 g.

M.p.: 59—60°C.

Example 12

2-[Bis-(2-chloroethyl)-amino]-3-(3-mesyloxypropyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 45.5 g. of N,N-bis-(β-chloroethyl)-phosphoric acid amide dichloride in 200 cc. of anhydrous dioxane is added to a solution of 41.8 g. of dipropanolamine and 57.7 g. of triethylamine in 200 cc. of anhydrous dioxane dropwise at room temperature within an hour. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is extracted with ether in a perforator. 2-[Bis-(2-chloroethyl)-amino]-3-(3-hydroxypropyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a colorless oil of medium viscosity.

Yield: 16 g. (30.5 g. of the theoretical).

A solution of 16 g. of the above compound and 5.5 g. of triethylamine in 45 cc. of anhydrous dioxane is added to a solution of 5.75 g. of methanesulfonyl chloride in 35 cc. of anhydrous dioxane dropwise within 35 minutes with cooling and stirring. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The resulting oil is extracted with anhydrous ether for 4 hours in a perforator. The ethereal extracts are evaporated and the resulting residue is dissolved in a mixture of methanol and water and the solution is allowed to stand for half an hour over Duolite (A-102). The resulting solution is filtered over activated charcoal and the solvent is evaporated in a water jet vacuum and dried in a high vacuum over P₂O₅. The product is obtained as a colorless oil.

Yield: 11.6 g.

n_D²¹: 1.5060.

Example 13

2-[Bis-(3-mesyloxypropyl)-amino]-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 26.6 g. of dipropanolamine and 26.4 g. of triethylamine in 100 cc. of methylene chloride is added to a solution of 38.8 g. of 2-chloro-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 120 cc. of methylene chloride dropwise within 40 minutes at a temperature ranging from 26—28°C. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated. The residue is extracted with ether in a perforator. 2-[Bis-(3-hydroxypropyl)-amino]-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a yellow oil.

Yield: 50.4 g. (99% of the theoretical).

A solution of 50.4 g of the above compound and 45 g. of triethylamine in 150 cc. of anhydrous methylene chloride is added to a solution of 46 g. of methanesulfonyl chloride in 100 cc. of methylene chloride dropwise with stirring within 45 minutes at a temperature ranging from 32—34°C. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is dissolved in 100 cc. of acetone. The solution is filtered and again evaporated. The resulting oil is dissolved in 250 cc. of chloroform. Thereafter, the solution is washed four times with 100 cc. of chilled water each time. The resulting product is dried over anhydrous sodium sulfate and then extracted with ether in a perforator.

The residue insoluble in ether is dissolved in 200 cc. of methylene chloride. The solution is filtered over activated charcoal and is evaporated. The desired final product is obtained as a yellow oil.

Yield: 30 g.

n_D^{20} : 1.4947.

Example 14

2-[Bis-(3-mesyloxypropyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 21 g. of triethylamine in 60 cc. of anhydrous dioxane is added to a solution of 37.5 g. of bis-(3-mesyloxypropyl)-amine hydrobromide and 21.8 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 200 cc. of anhydrous dioxane dropwise within 60 minutes at a temperature ranging from 35–40°C. The resulting reaction mixture is allowed to stand at room temperature for 16 hours. Thereafter, the separated mixture of triethylammonium halides is filtered off with suction and the filtrate is evaporated in a water jet vacuum.

The resulting oil is dissolved in 200 cc. of chloroform. The solution is washed five times with 50–60 cc. of chilled water each time and thereafter is dried over anhydrous sodium sulfate and again evaporated. The resulting oil is extracted with anhydrous ether for 2 hours in a perforator. The insoluble residue is dissolved in methylene chloride and the solution is filtered over activated charcoal and again evaporated. The product is dried in a high vacuum and is obtained as a yellow oil of high viscosity.

Yield: 17.6 g.

n_D^{21} : 1.5050.

Example 15

2-[(3-Mesyloxypropyl)-(2-chloroethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 20.4 g. of 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 100 cc. of chloroform is added to a solution of 16.4 g. of N-(3-hydroxypropyl)-N-(2-chloroethyl)-amine hydrochloride and 19.6 g. of triethylamine in 120 cc. of chloroform dropwise at 26°C. within an hour. Stirring is continued for 2–3 hours. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is extracted in a perforator with ether. 2-[(3-Hydroxypropyl)-(2-chloroethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as a colorless oil of medium viscosity.

Yield: 20.6 g. (69% of the theoretical).

A solution of 20.6 g. of the above compound and 7.3 g. of triethylamine in 100 cc. of anhydrous dioxane is added to a solution of 7.45 g. of methanesulfonyl chloride in 70 cc. of anhydrous dioxane dropwise within 30 minutes at 30°C. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated to half of its volume. Thereafter, 40 cc. of ether are added and the resulting solution is allowed to stand in an ice-box for several hours in order to precipitate further impurities. The solution is filtered and then evaporated. The resulting oil is washed with petrol ether in a perforator. The purified oil is dissolved in chloroform and the solution is washed once with sodium bicarbonate and three times with water. The solution is dried over anhydrous sodium sulfate and is again evaporated. The final step of evaporation is done in a high vacuum. The final product is obtained as a yellow oil.

Yield: 20.5 g.

n_D^{26} : 1.5048.

Example 16

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-thione

12.0 g. (1/20 mole) of 2-thiono-2-ethyleneimino-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine are dissolved in 450 cc. of anhydrous ether. A solution of 4.8 g. of methanesulfonic acid in 30 cc. of anhydrous ether is added with stirring and with the exclusion of air moisture dropwise with such a speed that the solution just gets turbid. The addition is finished after about 1.5 hours. The resulting product is precipitated in a thick layer on the walls of the reaction vessel and is filtered off with suction, washed with anhydrous ether and dried in a high vacuum over P_2O_5 . These steps too are carried out with the exclusion of air moisture. The product is very hygroscopic.

Yield: 8.5 g. (more than 50.4% of the theoretical).

M.p.: 42–45°C. (with decomposition).

Example 17

2-(2-Chloroethylamino)-3-(2-mesyloxyethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 26.5 cc. of HCl in ether (159.7 mg./cc.) is added to a solution of 32.9 g. of 2-ethyleneimino-3-(2-mesyloxyethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 175 cc. of anhydrous methylene chloride dropwise with vigorous stirring within 20 minutes at 30°C. Thereafter, the methylene chloride phase is decanted off from the highly viscous precipitate. The methylene chloride solution is filtered over activated charcoal and evaporated in a vacuum. The resulting oil is dissolved in methylene chloride and ether is added in such an amount to yield a methylene chloride: ether proportion of 1:1. The precipitated oil is again dissolved in methylene chloride and ether is added as previously and these steps are repeated until the precipitated oil is no more soluble in methylene chloride. The combined methylene chloride/ether extracts are filtered over activated charcoal and evaporated in a vacuum. The resulting oily product is dissolved in methylene chloride and the solution is washed three times with chilled water and dried. The solvent is evaporated, thus yielding into a yellow viscous oil.

Yield: 20.8 g.

n_D^{25} : 1.4967.

Example 18

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-5,5-dimethyl-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A solution of 43 g. of 2-chloro-3-(2-chloroethyl)-5,5-dimethyl-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide in 160 cc. of dry dioxane are added to a solution of 10.6 g. of ethanalamine and 17.8 g. of triethylamine in 130 cc. of anhydrous dioxane dropwise at 50°C. within an hour. The resulting mixture is heated at 80°C. for an additional period of 4 hours and is then allowed to stand at room temperature overnight. The separated triethylamine hydrochloride is filtered off with suction and the solution is evaporated in a water jet vacuum. The residue is extracted with ether in a perforator. The resulting 2-(2-hydroxyethylamino)-3-(2-chloroethyl)-5,5-dimethyl-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide is obtained as a colorless oil.

Yield: 27.1 g. (57.5% of the theoretical).

A solution of 27.1 g. of the above compound and 10.2 g. of triethylamine in 120 cc. of anhydrous dioxane is added to a solution of 11.5 g. of methanesulfonyl chloride in 90 cc. of anhydrous dioxane with stirring within 20 minutes. 75 cc. of ether are added to the resulting reaction mixture and the precipitated triethylamine hydrochloride is filtered off after standing for 1 hour. The solvent is evaporated and the resulting oil is extracted in a perforator three times with a 1:3 mixture of methylene chloride and ether. The thus purified product is a colorless, highly viscous oil.

Yield: 15.8 g.

n_D^{25} : 1.4912.

Example 19

2-(2-Ethylsulfonyloxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A solution of 24.3 g. of 2-(2-hydroxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide (prepared as described in Example 1) and 10.1 g. of triethylamine in 60 cc. of anhydrous dioxane is added to a solution of 12.9 g. of ethanesulfonyl chloride in 70 cc. of anhydrous dioxane dropwise with stirring within 20 minutes at a temperature ranging from 28—30°C. The reaction mixture is allowed to stand for 1 hour. Thereafter, the precipitated triethylamine hydrochloride is filtered off with suction. The solvent is evaporated in a vacuum and the resulting oily residue is purified by first extracting in a perforator with ether and then with a 2:1 mixture of methylene chloride and ether. The first ethereal extract is discarded. The solvents are evaporated from the methylene chloride/ether extracts and the resulting product crystallizes upon standing in the ice-box. The compound is recrystallized from methanol/ether.

Yield: 10 g.

F.: 62—64°C.

Example 20

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-2H-1,3,2-oxazaphospholidine-2-oxide

A solution of 7.45 g. of methanesulfonic acid in 40 cc. of anhydrous dioxane is added to a solution of 16.3 g. of 2-ethyleneimino-3-(2-chloroethyl)-2H-1,3,2-oxazaphospholidine-2-oxide in 80 cc. of anhydrous dioxane dropwise within 25 minutes at a

temperature ranging from 25—28°C. After the addition is finished the reaction mixture is heated to a temperature ranging from 35—40°C. The solvent is evaporated in a vacuum. The oily residue is extracted in a perforator first with ether for 1 hour and thereafter with a 1:1 mixture of methylene chloride and ether. The residue resulting from evaporation of the extract is purified chromatographically as described in Example 2. The desired product is obtained as a colorless oil.

Yield: 7.5 g.

n_D^{25} : 1.4963.

Example 21

2-(2-Mesyloxyethylamino)-3-(2-chloroethyl)-6-methyl-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A solution of 10.6 g. of 2-chloro-3-(2-chloroethyl)-6-methyl-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 50 cc. of anhydrous dioxane is added to a solution of 2.8 g. of ethanolamine and 4.6 g. of triethylamine in 50 cc. of anhydrous dioxane dropwise at 20°C. Stirring is continued for another 6 hours at room temperature. The precipitated triethylamine hydrochloride is filtered off with suction. The filtrate is evaporated in a water jet vacuum and the residue is washed with ether several times. Thereafter, the product is extracted in a perforator with ether. 2-(2-Hydroxyethylamino)-3-(2-chloroethyl)-6-methyl-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide is obtained as a yellow oil.

Yield: 7 g. (59.4% of the theoretical).

A solution of 3.1 g. of methanesulfonyl chloride in 30 cc. of anhydrous dioxane is added to a solution of 7 g. of the above compound and 2.8 g. of triethylamine in 150 cc. of anhydrous dioxane dropwise with stirring and cooling. The precipitated triethylamine hydrochloride is filtered off with suction and the resulting solution is filtered over activated charcoal. Thereafter, the solvent is distilled off in a vacuum. The residue is three times shaken with ether and the ethereal extracts are allowed to stand in the ice-box for several days. The precipitated product is filtered off and recrystallized from a 1:1 mixture methylene dichloride and ether.

Yield: 2 g. (22% of the theoretical).

M.p.: 104°C.

Example 22

2-(2-Mesyloxyethylamino)-3-ethyl-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 9.6 g. of methanesulfonic acid is added to a solution of 19 g. of 2-ethyleneimino-3-ethyl-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide in 200 cc. of anhydrous ether dropwise with stirring at a temperature ranging from 5—10°C. until a pH within 3—4 is reached. Stirring is continued for 15 minutes and the supernatant ethereal layer is decanted from the separated oil. The oil is dissolved in anhydrous methylene chloride. The solution is filtered over activated charcoal and evaporated in a water jet vacuum. The residue is extracted in a perforator with 250 cc. of a 1:1 mixture of ether and methylene chloride. Upon standing in the ice-box, the final product separates as crystals. The product is recrystallized from a mixture of ether and methylene chloride.

Yield: 9 g.

F.: 104°C.

Example 23

2-[(2-Mesyloxyethyl)-(2-chloroethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 11.4 g. of triethylamine in 60 cc. of methylene chloride is added to a suspension of 12 g. N-(2-mesyloxyethyl)-N-(2-chloroethyl)-phosphoric acid amide dichloride and 6.5 g. of N-(3-hydroxypropyl)-N-(2-chloroethyl)-amine hydrochloride in 90 cc. of methylene chloride dropwise with stirring within 15 minutes at 25°C. and with cooling when necessary. Stirring at room temperature is continued for 4 hours. The resulting reaction mixture is evaporated in a water jet vacuum. Anhydrous dioxane is added to the residue and precipitated triethylamine hydrochloride is filtered off with suction. The filtrate is filtered over activated charcoal and again evaporated in a water jet vacuum. The resulting oil is dissolved in methylene chloride and the solution is alternatively washed two times with ice-water, 0.01 N hydrochloric acid and a dilute sodium bicarbonate solution. The thus treated methylene chloride solution is dried over anhydrous sodium sulfate and is evaporated in a water jet vacuum. The resulting

oil is extracted several times with anhydrous ether and is finally dried in a high vacuum. The final product is obtained as a faintly yellow oil.

Yield: 5.7 g.

n_D^{25} : 1.0538.

Example 24

2-[(3-Mesyloxypropyl)-(2-chloroethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

12 g. of N-(3-mesyloxypropyl)-N-(2-chloroethyl)-phosphoric acid amide dichloride are dissolved in 60 cc. of methylene chloride and 6.3 g. of N-(3-hydroxypropyl)-N-(2-chloroethyl)-amine hydrochloride are suspended therein. A solution of 11 g. of triethylamine in 60 cc. of methylene chloride are added to the above suspension dropwise with stirring and cooling at 25°C. Thereafter, stirring is continued at room temperature for another 4 hours. The solvent is evaporated in a water jet vacuum. The residue is triturated with anhydrous dioxane and the separated triethylamine hydrochloride is filtered off with suction. The filtrate is filtered over activated charcoal and again evaporated in a water jet vacuum. The resulting oil is shaken three times with anhydrous ether and thereafter is dried in a high vacuum. The desired final product is obtained as a yellowish oil.

Yield: 6.1 g.

n_D^{25} : 1.5046.

Example 25

2-(2-Propylsulfonyloxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A solution of 24.3 g. of 2-(2-hydroxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide (prepared as described in Example 1) and 10.1 g. of triethylamine in 170 cc. of anhydrous dioxane is added dropwise to a solution of 14.3 g. of n-propanesulfonyl chloride in 70 cc. of anhydrous dioxane dropwise with stirring and cooling within 15 minutes at a temperature ranging from 28—30°C. Stirring is continued for a short period of time at 30°C. Thereafter, 60 cc. of anhydrous ether are added, the mixture is cooled to 10°C. and stirring is continued for another half hour. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is filtered over activated charcoal and evaporated in a water jet vacuum. The oily residue is extracted in a perforator with a 1:1 mixture of ether and methylene chloride. The extract is allowed to stand in the ice-box and is scratched several times thus causing the desired product to crystallize. The crystals are recrystallized from the same solvent mixture.

Yield: 14 g.

F.: 78°C.

Example 26

2-[Bis-(2-mesyloxyethyl)-amino]-3-(2-mesyloxyethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 10.9 g. of N-2-chloroethyl-aminopropanol and 20 g. of triethylamine in 150 cc. of chloroform is added to a solution of 16.1 g. of N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride in 50 cc. of chloroform dropwise at 20°C. within 1 hour. The reaction mixture thereafter is heated to boiling for several hours. After cooling at 0°C. the separated triethylamine hydrochloride is filtered off with suction. The filtrate is evaporated and the resulting residue is triturated with ether. The resulting suspension is filtered and the filtrate is again evaporated. Thus, 2-[bis-(2-chloroethyl)-amino]-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide is obtained as an oil which solidifies upon seeding.

Yield: 16.2 g. (80% of the theoretical).

F.: 50—51°C.

A solution of 16.2 g. of the above compound and 36.6 g. of silver methane sulfonate in 150 cc. of anhydrous acetonitrile are refluxed for 24 hours with the exclusion of light. The precipitated silver chloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The residue is triturated in methylene chloride. The resulting mixture is filtered and the filtrate is shaken twice consecutively with chilled water, 0.01 N hydrochloric acid and dilute sodium bicarbonate solution. The thus treated filtrate is dried over anhydrous sodium sulfate and filtered over activated charcoal. The resulting solution is again evaporated in a high vacuum, the residue is shaken several times with anhydrous ether and the resulting oil is dried in a high vacuum. The desired final product is obtained as a colorless oil.

Yield: 10.8 g.

n_D^{25} : 1.4905.

Example 27

2-(2-Isopropylsulfonyloxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A mixture of 24.3 g. of 2-(2-hydroxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide (prepared as described in Example 1) and 10.5 g. of triethylamine in 75 cc. of dioxane are added to a solution of 14.3 g. of isopropane-sulfonyl chloride in 70 cc. of dioxane dropwise within 25 minutes at a temperature ranging from 28—30°C. The separated triethylamine hydrochloride is filtered off with suction. The solvent is evaporated in a water jet vacuum and the oily residue is washed with ether in a perforator for 2 hours. Thereafter, it is extracted twice with a mixture of methylene chloride and ether. The extracts are filtered over activated charcoal and evaporated. Thus, a clear yellowish and highly viscous oil is obtained which is purified chromatographically over a column of silica gel in methylene chloride.

Yield: 16.4 g. (47% of the theoretical)

n_D^{20} : 1.4927.

Example 28

2-(2-n-Pentylsulfonyloxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A solution of 24.3 g. of 2-(2-hydroxyethylamino)-3-(2-chloroethyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide (prepared as described in Example 1) and 10.5 g. of triethylamine in 90 cc. of dioxane is added to a solution of 17.1 g. of n-pentane sulfonyl chloride in 75 cc. of dioxane dropwise with thorough stirring and cooling such that the temperature does not rise above 35°C. Stirring is continued for another half an hour. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The resulting oil is dissolved in chloroform and washed with dilute hydrochloric acid, a sodium bicarbonate solution and water. The thus treated solution is again evaporated. The residue is extracted with ether in a perforator. The ethereal extract is allowed to stand in an ice-box whereupon the desired final product crystallizes. It is recrystallized from ether.

Yield: 10.5 g. (27.8% of the theoretical)

F.: 59—60°C.

Example 29

2-(2-Mesyloxyethylamino)-3-(3-chloropropyl)-2H-tetrahydro-1,3,2-oxazaphosphorine-2-oxide

A solution of 5.1 g. of dipropanolamine and 11.6 g. of triethylamine in 150 g. of methylene dichloride are added to a solution of 9.8 g. of N-(2-mesyloxyethyl)-phosphoric acid amide dichloride in 50 cc. of methylene dichloride dropwise with stirring at 25°C. and with cooling as necessary. Stirring is continued at room temperature for another hour. The solvent is distilled off in a water jet vacuum and triethylamine hydrochloride is precipitated by the addition of dioxane and is filtered off. The filtrate is again evaporated in a high vacuum. The oily residue is dissolved in 80 cc. of chloroform without further purification. A solution of 13 cc. of thionyl chloride in 20 cc. of chloroform is added thereto with stirring. After completion of the reaction, the solution is washed with 0.1 N hydrochloric acid and thereafter with dilute sodium bicarbonate solution. It is then dried over anhydrous sodium sulfate. The solvent is distilled off and the residue is purified chromatographically as described in Example 9.

Yield: 8 g. (60% of the theoretical)

F.: 92—93°C.

Example 30

2-(2-Mesyloxypropylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

A solution of 11.5 g. (1/10 mole) of methanesulfonyl chloride in 70 cc. of anhydrous dioxane are added to a solution of 25.7 g. (1/10 mole) of 2-(2-hydroxy-propylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide (prepared from 2-hydroxy-propylamine and 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide as described in Example 1) and 10.5 g. (1/10 mole) of triethylamine in 60 cc. of anhydrous dioxane dropwise with stirring within 20 minutes at a temperature within a range of 28—30°C. The separated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The resulting oil is extracted in a perforator for about 1 hour with a 1:1 mixture of ether and methylene chloride. Upon standing in an ice-bath, colorless crystals separate from the thus treated solution. The crystals are recrystallized from the same solvent mixture of ether:methylene chloride (5:1).

Yield: 22.4 g. (67% of the theoretical)

M.p.: 100—101°C.

Example 31

2-(1-Ethyl-2-mesyloxyethylamino)-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

5 A solution of 11.5 g. (1/10 mole) of methanesulfonyl chloride in anhydrous dioxane is added dropwise to a solution of 27 g. (1/10 mole) of 2-(1-ethyl-2-hydroxy-ethylamino) - 3 - (2 - chloroethyl) - tetrahydro - 2H - 1,3,2 - oxazaphosphorine - 2 - oxide (prepared from 1-ethyl-2-hydroxy-ethylamine and 2-chloro-3-(2-chloroethyl)-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide as described in Example 1) and 10.5 g. (1/10 mole) of triethylamine in 65 cc. of anhydrous dioxane dropwise with stirring within 20 minutes at a temperature within the range of 28—32°C. The precipitated triethylamine hydrochloride is filtered off with suction and the filtrate is evaporated in a water jet vacuum. The remaining oil solidifies upon standing for a short period of time. It is recrystallized twice from isopropanol. The desired final product is obtained as colorless crystals.

15 Yield: 21.0 g. (60% of the theoretical)
M.p.: 129—130°C.

Example 32

The following recipe is used for the production of 100,000 dragees containing each 50 mg. of the active compound according to the present invention:

20	Compound according to Example 1	5.000 kg.	20
	Corn starch	4.000 kg.	
	Lactose	4.115 kg.	
	Polyvinylpyrrolidone	0.060 kg.	
	Talcum	0.575 kg.	
25	Magnesium stearate	0.250 kg.	25
		14.000 kg.	

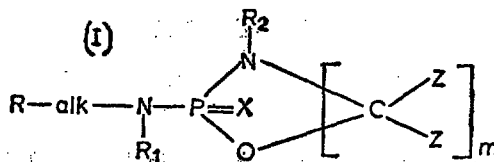
30 The crystalline active compound is passed together with 3 kg. of corn starch through a sieve having a mesh size of 1 mm. The products are thoroughly mixed and a paste is formed with a 10% solution of the polyvinylpyrrolidone in isopropanol. The moist product is granulated by passing it through a sieve having a mesh size of 3 mm. It is then dried and ground to a particle size of 1 mm. Finally, the remaining auxiliary products of the above recipe are sieved and thoroughly admixed and 100 000 dragees are pressed each weighing 140 mg., having a diameter of 7 mm. and a camber diameter of 6 mm. The resulting kernels are coated in manner known per se by first applying a layer resistant to the gastric juices giving each kernel a weight of 170 mg., then applying a cover until the kernel weight is 205 mg., smoothing the surfaces of the kernels until the kernel weight is 215 mg. and thereafter applying colouring layers up to a kernel weight of 240 mg. Finally, the coated kernels are rendered glossy by applying a layer of hard wax.

Example 33

40 A dry mix of active compound and sodium chloride is filled into a glass for the production of injection solutions. In the last step of purification by recrystallization of the active compound according to Example 1, the solution thereof is passed through a filter holding back germs. The further processing is effected under aseptic conditions. The crystallized compound is separated by centrifugation and dried and held in an atmosphere of ethylene oxide. A sample is taken and checked for purity and sterility. After clearance for further processing is obtained, the compound is mixed with sterile sodium chloride p.a. in a weight proportion of 100 to 45 under aseptic conditions, thus producing a finely divided homogenous mix. Another sample is taken and tested for its content of active compound, for sterility and freedom from pyrogenous compounds. After clearance for further processing, 145 mg. of the mix are filled into flasks of 10 ml. each under aseptic conditions and in an atmosphere of nitrogen. The flasks are closed with aseptic stoppers of butyl cabotsachouc. The final check is made in accordance with the recommendations of the Section "Testing for good quality and sterility" of the German Federal Health Administration. In order to produce injection solutions, 5 cc. of water purified for injection solutions are added to the content of a flask which is dissolved therein.

WHAT WE CLAIM IS:—

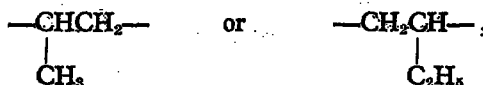
1. Alkyl sulfonic acid esters of 1,3,2-oxazaphosphacyclic compounds of formula I



wherein R represents a halogen atom or an alkyl sulfonyl group having a straight or branched alkyl chain with 1 to 6 carbon atoms; R_1 and R_2 each represent hydrogen or an alkyl group having from 1 to 4 carbon atoms which may be substituted with a halogen atom or with an alkylsulfonyl group having a straight or branched alkyl chain with 1 to 6 carbon atoms, R_1 and R_2 being identical or different from each other; there being at least one alkylsulfonyl group present in the molecular of formula I; and alk represents a straight or branched alkylene group having 2 or 3 carbon atoms in a chain intervening between the group R and the N atom and, if branched, having a total number of 3 or 4 carbon atoms; X represents oxygen or sulphur; each Z independently represents hydrogen or an alkyl group with 1 to 4 carbon atoms; and m is 2 or 3.

2. A compound as claimed in claim 1 wherein X is oxygen, Z is hydrogen and m is 3.

3. A compound as claimed in claim 2 wherein R is an alkylsulfonyl group having a straight or branched alkyl chain with 1 to 6 carbon atoms, R_1 is hydrogen, R_2 is the β -chloroethyl group and alk is $-\text{CH}_2\text{CH}_2-$,



4. A compound as claimed in claim 3 wherein alk is $-\text{CH}_2\text{CH}_2-$ and R is the methylsulfonyl group $\text{CH}_3\text{SO}_2\text{O}-$ or the ethylsulfonyl group $\text{C}_2\text{H}_5\text{SO}_2\text{O}-$ or alk is

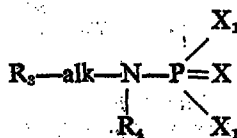


and R is the methylsulfonyl group $\text{CH}_3\text{SO}_2\text{O}-$.

5. Alkyl sulphonic acid esters of 1,3,2-oxazaphosphacyclic compounds as claimed in claim 1 as hereinbefore described with reference to any of Examples 1 to 31.

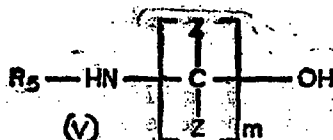
6. A process for the production of the alkyl sulfonic acid esters of 1,3,2-oxazaphosphacyclic compounds as claimed in claims 1 to 4 comprising

A) subjecting a compound of formula IV



IV

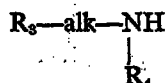
wherein R_3 has the same meaning as R in formula I or is a hydroxy group, R_1 has the same meaning as R_1 in formula I or is an alkyl group having from 1 to 4 carbon atoms and being substituted by a hydroxy group, alk and X have the same meaning as in formula I and X_1 is a halogen atom, to reaction with a compound of formula V





wherein R_5 has the same meaning as R_4 in formula IV and Z and m have the same meaning as in formula I, or

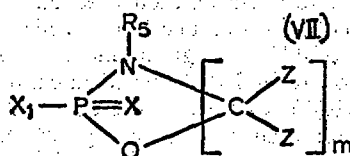
B) subjecting a compound of formula VI



VI

5 wherein R_5 and R_4 have the same meaning as in formula IV and alk has the same meaning as in formula I, to reaction with a compound of formula VII

5

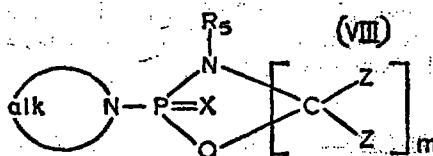


wherein X_1 has the same meaning as in formula IV, R_5 has the same meaning as in formula V and X , Z and m have the same meaning as in formula I, or

10

C) subjecting a compound of formula VIII

10



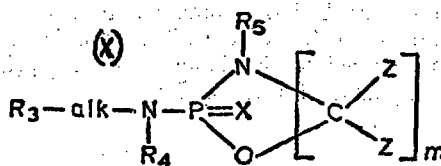
wherein R_5 has the same meaning as in formula V and X , Z , alk and m have the same meaning as in formula I, to reaction with a compound of formula IX



IX

15 wherein R_6 has the same meaning as in formula IV, and converting the hydroxy groups in the resulting compound of formula X

15



20 whenever one or more of the substituents R_3 , R_4 and R_5 represent or carry an hydroxy group, into halogen atom(s) or group(s) $-\text{OSO}_2R_6$, R_6 being a straight or branched alkyl group having from 1 to 6 carbon atoms, and, if desired, replacing one or more of any halogen atoms in the resulting compound of formula X, wherein none of the substituents R_3 , R_4 and R_5 represent or carry a hydroxy group but where one or more of the substituents R_3 , R_4 and R_5 represent or carry a halogen atom, with $-\text{OSO}_2R_6$ group(s) by subjecting said compound of formula X to reaction with a compound of formula XI:

25

25



XI

wherein R_6 has the above given meaning and Me is a metal of the first or second main or sub-groups of the periodic system of elements.

7. A pharmaceutical preparation comprising a compound as claimed in any of

claims 1 to 4 as the active ingredient and a solid or liquid pharmaceutically acceptable carrier or diluent.

8. A pharmaceutical preparation as hereinbefore described and with reference to either of the Examples 32 or 33.

ELKINGTON & FIFE,
Chartered Patent Agents,
High Holborn House,
52/54 High Holborn,
London, WC1V 6SH.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1973.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

