

Aromatic derivatives of phosphonoformic acid, processes for their preparation, pharmaceutical compositions containing them and their use for combating virus infections

FIELD OF THE INVENTION

The present invention relates to novel compounds, methods for their preparation, novel pharmaceutical compositions and to their use for selectively combating viruses such as herpes viruses, influenza viruses, RNA tumor viruses, etc., which can cause various diseases in animals including man.

5 Such diseases include both common infections and neoplastic diseases, i.e. cancer.

BACKGROUND OF THE INVENTION

The effects of viruses on bodily functions is the end result of changes occurring at the cellular and subcellular levels. The pathogenic changes at the cellular level are different for different combinations of viruses and host cells. While some viruses cause a general destruction (killing) of certain cells, other may transform cells to a neoplastic state.

Important common viral infections are herpes dermatitis (including herpes labialis), herpes keratitis, herpes genitalis, herpes zoster, herpes encephalitis, infectious mononucleosis and cytomegalovirus infections all of which are caused by viruses belonging to the herpesvirus group. Other important viral diseases are influenza A and B which are caused by influenza A and B virus respectively. Another important common viral disease is viral hepatitis and especially hepatitis B virus infections are widely spread. Effective and selective antiviral agents are needed for the treatment of these diseases.

Several different viruses of both DNA and RNA type have been shown to cause tumors in animals. The effect of cancerogenic chemicals can on animals result in activation of latent tumor viruses. It is possible that tumor viruses are involved in human tumors. The most likely human cases known today are leucemias, sarcomas, breast carcinomas, Burkitt lymphomas, nasopharyngeal carcinomas and cervical cancers where RNA tumor viruses and herpes viruses are indicated. This makes the search for selective inhibitors of tumorogenic viruses and their functions an important undertaking in the efforts to treat cancer.

A most important common feature of the interaction between viruses and cells is the replication or transcription of the specific viral genetic information carried by viral nucleic acids. These viral nucleic acids are of two kinds, deoxyribonucleic acids (DNA) or ribonucleic acids (RNA). The primary genetic information of the cell is carried by cell DNA. DNA and RNA synthesis involves complex enzymes called DNA and RNA polymerases respectively. The genetic information is transferred to the new nucleic acid from a template nucleic acid. There are four general ways in which these nucleic acids can be replicated or transcribed.

- | | | | | |
|----|-------------------|---------------------------------|---|-----|
| 35 | 1. DNA (template) | DNA-dependent
DNA polymerase | → | DNA |
| | 2. RNA (template) | RNA-dependent
RNA polymerase | → | RNA |
| 40 | | | | |
| | 3. DNA (template) | DNA-dependent
RNA polymerase | → | RNA |
| 45 | | | | |
| | 4. RNA (template) | RNA-dependent
DNA polymerase | → | DNA |
| 50 | | (reverse transcriptase) | | |

Processes 1 and 3 are used by cells. DNA viruses such as herpesviruses also use process 1 but the enzyme is different from that of the cell. RNA viruses such as influenza virus use process 2 and the RNA tumor viruses (retroviruses) can transcribe its RNA to DNA according to process 4.

The viral polymerases and the viral nucleic acid syntheses are essential not only for ordinary (productive) virus infections but also for viral transformation of cells to a neoplastic state leading to cancer (tumorogenic function of virus). In the latter case DNA produced by DNA viruses such as herpesvirus or transcribed from RNA tumor viruses and which carries the genetic information for cell transformation can be integrated into the host cell DNA. This integration, or later acts as a consequence of integration (such as interaction with cancerogenic chemicals), can then lead to the transformation of the host cell. The implications of inhibiting reverse transcriptase for cell transformation are also described in U.S. patent 3,979,511.

Since the viral polymerases in most cases differ from the cellular ones these viral enzymes and viral nucleic acid syntheses are good targets for specific antiviral chemotherapy including chemotherapy of cancer caused by viruses. It should be noted that many compounds presently used for chemotherapy of cancer are inhibitors of nucleic acid synthesis. It is therefore possible that antiviral compounds which are also inhibitors of nucleic acid synthesis can affect tumor cells directly. There is a need for an effective antiviral agent preferably having a selective inhibiting effect on a specific viral function of the virus to be combated. It is, therefore, a general object of the present invention to provide a novel method for combating virus infections using an antiviral agent which exerts a selective inhibiting effect on viral functions but which exerts only a negligible inhibiting effect on functions of the host cells.

PRIOR ART

Patent No. 77.666 in Luxemburg discloses phosphonoformic acid as having antiviral activity. Unlisted Drugs Vol. 17. No. 12, page 89 article m (1965) discloses dimethylcarbethoxy-phosphonate as slightly mitotic in vitro.

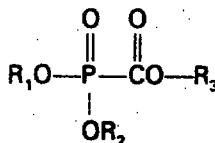
French patent application No. 74 25333 (Publication No. 2238432) discloses phosphonoformic acid and a number of derivatives thereof as having plant growth regulating properties.

Chemical Abstracts vol. 50 page 794d (1956) discloses i.a. certain esters of phosphonoformic acid as chemical entities. Reference is made also to European patent application 78 85 0028.8, publication number 0 003 007, which is not prior art but which discloses and claims a number of esters of phosphonoformic acid as antivirally active compounds.

Various esters of phosphonoformic acid are described in for example US Patent Nos. 3 943 201, 3 155 597, 3 533 995 and in Chem. Ber. 57, P 1023 (1924). However, these ester have not been suggested for any pharmacological use. Moreover, the chemical structure of the esters of the present invention is different from that of the prior known esters. More particularly, the novel esters are exclusively esters of phenols.

THE INVENTION

It has been found according to the present invention that the compounds of the formula



wherein each of R_1 , R_2 and R_3 , which are the same or different, is hydrogen or a phenyl group of the formula



wherein each of R_4 and R_5 , which are the same or different, is selected from the group consisting of hydrogen, halogen, alkyl having 1, 2, or 3 carbon atoms, alkoxy having 1, 2, or 3 carbon atoms, alkoxy-carbonyl having 2—7 carbon atoms; or alkylcarbonyl having 2—7 carbon atoms; or R_4 and R_5 together form a straight saturated alkylene chain having 3 or 4 carbon atoms and being bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring; provided that one of R_1 and R_2 is a phenyl group of the formula II when R_3 is H; and physiologically acceptable salts thereof, inhibit certain viral functions including tumorigenic functions and the multiplication of viruses.

The compounds of the formula I and physiologically acceptable salts thereof are useful in therapeutic and/or prophylactic treatment of viral diseases and may be useful in therapeutic and/or prophylactic treatment of cancer caused by viruses.

It is understood that the reference to "physiologically acceptable salts" of the compounds of the formula I in the present specification and claims relates only to such compounds which can form salts. Compounds wherein at least one of R_1 , R_2 and R_3 is hydrogen can form salts. Compounds wherein all of R_1 , R_2 and R_3 are different from hydrogen do not form salts.

Since the compounds of the formula I, when R_1 and R_2 are different, contain an asymmetric center, they exist in the form of optically active forms, and can be resolved into their optical antipodes by known methods.

In this specification, the compounds of the invention are named as derivatives of the compound hydroxycarbonylphosphonic acid, which compound also is known under the name phosphonoformic acid.

The provision in the definition of the compounds of the invention means that the radicals R_1 , R_2

and R_3 in formula I can be combined as illustrated in the following tabulation. It is understood that R_1 and R_2 , which are the same or different, are considered as equivalent and interchangeable in the table below.

R_1	R_2	R_3
H	phenyl group of formula II	H
phenyl group of formula II	phenyl group of formula II	phenyl group of formula II
H	phenyl group of formula II	phenyl group of formula II
H	H	phenyl group of formula II

The compounds of the formula I and physiologically acceptable salts thereof are useful in therapeutic and/or prophylactic treatment of viral diseases and may be useful in therapeutic and/or prophylactic treatment of cancer caused by viruses.

25 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides

- A. A compound of the formula I or a physiologically acceptable salt thereof for use in the treatment of diseases caused by viruses in animals including man.
- B. A compound of the formula I or a physiologically acceptable salt thereof for use in the treatment of virus-induced neoplastic diseases in animals including man, by inhibiting the transformation of virus-infected cells.
- C. A compound of the formula I or a physiologically acceptable salt thereof for use in the treatment of diseases caused by viruses in animals including man, by inhibiting the activity of viral polymerase.
- D. A compound of the formula I or a physiologically acceptable salt thereof for use in inhibiting the activity of reverse transcriptases of viruses in animals including man.
- E. A compound of the formula I or a physiologically acceptable salt thereof for use in inhibiting the multiplication of virus, in particular herpesviruses, influenza virus and hepatitis B virus, and retroviruses in animals including man.
- F. A compound of the formula I or a physiologically acceptable salt thereof for use in inhibiting the growth of virus-transformed cells in animals including man.
- G. A compound of the formula I or a physiologically acceptable salt thereof for use in the treatment of virus-induced neoplastic diseases in animals including man, by inhibiting the multiplication of tumor viruses.
- H. A compound of the formula I or a physiologically acceptable salt thereof for use in the treatment of virus-induced neoplastic diseases in animals including man by inhibiting the activity of reverse transcriptase.
- I. A compound of the formula I or a physiologically acceptable salt thereof for use in the treatment of neoplastic diseases in animals including man.

For example, the invention relates to the use of a compound of the formula I or a physiologically acceptable salt thereof, for

- (a) inhibiting the replication of virus in animals including man, in particular herpesvirus, influenza virus and hepatitis B viruses, and
- (b) for inhibiting the growth of virus-transformed cells in animals including man.

Furthermore, the invention provides pharmaceutical preparations comprising as active ingredient a compound of the formula I or a physiologically acceptable salt thereof, optionally in association with a pharmaceutically acceptable carrier.

The compounds within the formula I are novel compounds. The invention also comprises the novel compounds *per se*.

Phosphonoformic acid and physiologically acceptable salts thereof inhibit viral functions such as polymerases including reverse transcriptase and virus multiplication, and have effects on virus infections and virus-related tumors in animal models. The antiviral effects of trisodium phosphonate is described by Helgstrand et al. Science 201, 819 (1978).

An important aspect of the invention is that the radicals R_1 , R_2 and R_3 in formula I can be chosen in such a way that the compounds of formula I and physiologically acceptable salts thereof possess more favourable pharmacokinetic properties than phosphonoformic acid and physiologically acceptable salts

thereof. Such favourable pharmacokinetic properties include better tissue penetration, better oral absorption and prolonged activity.

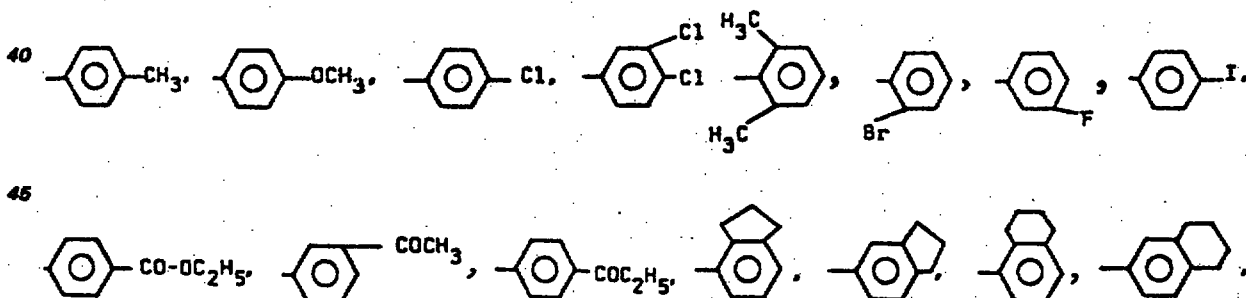
Although the present invention relates broadly to a novel method for selectively combating viral diseases in animals and man, and pharmaceutical preparations to be used in such treatment, it will be particularly useful in the treatment of herpesvirus infections, influenza virus infections, hepatitis B virus infections and cancer caused by herpesviruses and RNA tumor viruses.

An especially important area of use for the compositions of the present invention is in the treatment of herpes virus infections. Among the herpesviruses may be mentioned Herpes simplex type 1 and 2, varicella (Herpes zoster), virus causing infectious mononucleosis (i.e. Epstein-Barr virus), and cytomegalovirus. Important diseases caused by herpes viruses are herpes dermatitis, (including herpes labialis), herpes genitalis, herpes keratitis and herpes encephalitis. Another important area of use for the compositions of the present invention is in the treatment of infections caused by orthomyxoviruses, i.e. influenza viruses of type A and type B. A further area of use is the treatment of infections caused by viruses such as hepatitis virus A and hepatitis virus B, papillomaviruses, adenoviruses and poxviruses.

Other possible areas of use for the compositions of the present invention are in the treatment of infections caused by picornaviruses, togaviruses including arboviruses, retroviruses (e.g. leucoviruses), arenaviruses, coronaviruses, rhabdoviruses, paramyxoviruses, hepatitis non A and non B virus, iridoviruses, papovaviruses, parvoviruses, reoviruses, and bunyaviruses.

Another possible area of use for the compositions of the present invention is in the treatment of cancer and tumors, particularly those caused by viruses. This effect may be obtained in different ways, i.e. by inhibiting the transformation of virus-infected cells to a neoplastic state, by inhibiting the spread of viruses from transformed cells to other normal cells and by arresting the growth of virus-transformed cells. A particular area of use for the compositions of the present invention is in the inhibition of reverse transcriptases of RNA tumor viruses. The viruses in this group include all of the transforming sarcoma C-type viruses, the leukemia C-type viruses and the mammary B-type viruses. Possible areas of use for the compositions of the present invention with respect to cancer chemotherapy are treatment of leucemias, lymphomas including Burkitt lymphomas and Hodgkin's disease, sarcomas, breast carcinoma, nasopharyngeal carcinomas and cervical cancers in which RNA tumor viruses and herpesviruses are indicated. Other possible areas of use for the composition of the present invention with respect to cancer chemotherapy are treatment of multiple myeloma and cancer of the lungs (and bronchus), the stomach, the liver, the colon, the bladder, the lips, the bones, the kidneys, the ovary, the prostate, the pancreas, the skin (melanoma), the rectum, the salivary glands, the mouth, the esophagus, the testis, the brain (and cranial meninges), the thyroid gland, the gallbladder (and ducts), the nose, the larynx, connective tissues, the penis, the vulvas, the vagina, the corpus uteri, the tongue, the breasts, and the cervix.

Illustrative examples of the meanings of the radicals R_1 , R_2 , and R_3 in the formula I above are: substituted phenyl:



50 or phenyl.

The above illustrative examples are intended to illustrate the meanings of all the radicals R_1 , R_2 and R_3 within the boundaries with regard to number of carbon atoms which may be prescribed for each radical.

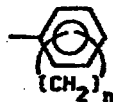
55 Preferred groups of the radicals R_1 and R_2 are:

1. Phenyl
2. monosubstituted phenyl groups
3. disubstituted phenyl groups
- 60 4. mono-alkyl substituted phenyl groups
5. mono-halogen substituted phenyl groups
6. mono-alkoxy substituted phenyl groups
7. mono-alkylcarbonyl substituted phenyl groups
8. mono-alkoxycarbonyl substituted phenyl groups
- 65 9. di-alkyl substituted phenyl groups

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- 10. di-halogen substituted phenyl groups
- 11. di-alkoxy substituted phenyl groups
- 12. alkyl and halogen substituted phenyl groups
- 13. alkyl and alkoxy carbonyl substituted phenyl groups
- 14. alkoxy and alkyl carbonyl substituted phenyl groups
- 15. phenyl groups of the formula

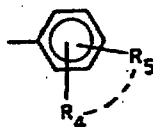
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wherein n is 3 or 4 and wherein the alkylene chain is bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring.

- 16. Particularly preferred groups of the radicals R_1 and R_2 are unsubstituted, monosubstituted and disubstituted phenyl groups within the above formula

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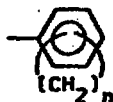


wherein R_4 and R_5 have the meanings given above.

- 25. In a preferred embodiment, R_1 and R_2 have the same meaning. Preferred groups of the radical R_3 are:

- 1. Phenyl
- 2. monosubstituted phenyl groups
- 30 3. disubstituted phenyl groups
- 4. mono-alkyl substituted phenyl groups
- 5. mono-halogen substituted phenyl groups
- 6. mono-alkoxy substituted phenyl groups
- 7. mono-alkyl carbonyl substituted phenyl groups
- 35 8. mono-alkoxy carbonyl substituted phenyl groups
- 9. di-alkyl substituted phenyl groups
- 10. di-halogen substituted phenyl groups
- 11. di-alkoxy substituted phenyl groups
- 12. phenyl groups of the formula

40



45

wherein n is 3 or 4 and wherein the alkylene chain is bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring.

- 13. alkyl and halogen substituted phenyl groups
- 50 14. alkyl and alkoxy carbonyl substituted phenyl groups
- 15. alkoxy and alkyl carbonyl substituted phenyl groups

Particularly preferred groups of the radicals R_3 are unsubstituted, monosubstituted and disubstituted phenyl groups within the above formula

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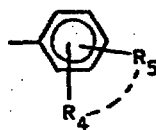
wherein R_4 and R_5 have the meanings given above. Preferred combinations of R_1 , R_2 and R_3 are:

- 65 1. R_1 , R_2 and R_3 are phenyl,

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2. R_1 and R_2 , which are the same or different, are unsubstituted, monosubstituted or disubstituted phenyl groups within the formula

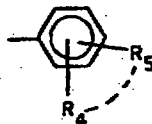
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10 wherein R_4 and R_5 have the meanings given above, and R_3 is phenyl.

3. R_1 , R_2 and R_3 are unsubstituted, monosubstituted or disubstituted phenyl groups within the formula

15



20 wherein R_4 and R_5 have the meanings given above,

4. R_1 and R_2 are hydrogen and R_3 is phenyl,

5. R_1 and R_2 are hydrogen and R_3 is a monosubstituted phenyl group,

6. R_1 and R_2 are hydrogen and R_3 is a disubstituted phenyl group,

7. R_1 and R_2 are hydrogen and R_3 is a mono-alkyl substituted phenyl group,

25 8. R_1 and R_2 are hydrogen and R_3 is a mono-halogen substituted phenyl group,

9. R_1 and R_2 are hydrogen and R_3 is a mono-alkoxy substituted phenyl group,

10. R_1 and R_2 are hydrogen and R_3 is a mono-alkoxycarbonyl substituted phenyl group,

11. R_1 and R_2 are hydrogen and R_3 is a mono-alkylcarbonyl substituted phenyl group,

12. R_1 and R_2 are hydrogen and R_3 is a di-alkyl substituted phenyl group,

30 13. R_1 and R_2 are hydrogen and R_3 is a di-halogen substituted phenyl group,

14. R_1 and R_2 are hydrogen and R_3 is a di-alkoxy substituted phenyl group,

15. R_1 and R_2 are hydrogen and R_3 is a phenyl group of the formula

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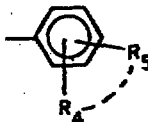


40 wherein n is 3 or 4 and wherein the alkylene chain is bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring,

16. R_1 is hydrogen and R_2 and R_3 are phenyl,

17. R_1 is hydrogen, R_2 is a monosubstituted or disubstituted phenyl group within the formula

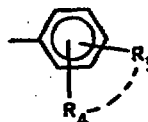
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50 wherein R_4 and R_5 have the meanings given above and R_3 is phenyl.

18. R_1 is hydrogen and R_2 and R_3 , which are the same or different, are monosubstituted or disubstituted phenyl groups within the formula

55



wherein R_4 and R_5 have the meanings given above,

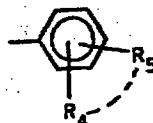
60 19. R_1 is hydrogen, R_2 is phenyl and R_3 is a monosubstituted or disubstituted phenyl group within the formula

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wherein R_4 and R_5 have the meanings given above,

20. R_1 is hydrogen, and R_2 and R_3 , which are the same or different are unsubstituted, mono-substituted or disubstituted phenyl groups within the formula



wherein R_4 and R_5 have the meanings given above,

21. R_1 and R_3 are hydrogen and R_2 is phenyl,
22. R_1 and R_3 are hydrogen and R_2 is a monosubstituted phenyl group,
23. R_1 and R_3 are hydrogen and R_2 is a disubstituted phenyl group,
24. R_1 and R_3 are hydrogen and R_2 is a mono-alkyl substituted phenyl group,
25. R_1 and R_3 are hydrogen and R_2 is a mono-halogen substituted phenyl group,
26. R_1 and R_3 are hydrogen and R_2 is a mono-alkoxy substituted phenyl group,
27. R_1 and R_3 are hydrogen and R_2 is a mono-alkoxycarbonyl substituted phenyl group,
28. R_1 and R_3 are hydrogen and R_2 is a mono-alkylcarbonyl substituted phenyl group,
29. R_1 and R_3 are hydrogen and R_2 is a di-alkyl substituted phenyl group,
30. R_1 and R_3 are hydrogen and R_2 is a di-halogen substituted phenyl group,
31. R_1 and R_3 are hydrogen and R_2 is a di-alkoxy substituted phenyl group,
32. R_1 and R_3 are hydrogen and R_2 is a phenyl group of the formula



wherein n is 3 or 4 and wherein the alkylene chain is bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring,

33. compounds of the formula I wherein R_1 and R_2 are hydrogen,
 34. compounds of the formula I wherein R_1 is hydrogen,
 35. compounds of the formula I wherein R_1 and R_3 are hydrogen.
- Examples of compounds of the invention are given in the following table.

R_1	R_2	R_3
H	H	phenyl
H	H	4-methylphenyl
H	H	4-methoxyphenyl
H	H	4-chlorophenyl
H	H	3,4-dichlorophenyl
H	H	4-ethoxycarbonylphenyl
H	phenyl	phenyl
H	4-chlorophenyl	phenyl
H	3,4-dichlorophenyl	phenyl
H	4-methoxyphenyl	phenyl
H	4-methylphenyl	phenyl
H	4-ethoxycarbonylphenyl	phenyl
H	phenyl	4-chlorophenyl
H	phenyl	3,4-dichlorophenyl

	R ₁	R ₂	R ₃
	H	phenyl	4-methoxyphenyl
5	H	phenyl	4-methoxyphenyl
	H	phenyl	4-ethoxycarbonylphenyl
10	H	4-chlorophenyl	4-methoxyphenyl
	H	4-chlorophenyl	4-methoxyphenyl
	H	4-chlorophenyl	4-ethoxycarbonylphenyl
15	H	4-chlorophenyl	
	H	4-methoxyphenyl	4-methoxyphenyl
20	H	4-methoxyphenyl	4-ethoxycarbonylphenyl
	H	4-methoxyphenyl	
25	H	4-methylphenyl	4-chlorophenyl
	H	4-methylphenyl	4-methoxyphenyl
30	H	4-methylphenyl	4-ethoxycarbonylphenyl
	phenyl	phenyl	phenyl
35	H	phenyl	H
	H	4-methylphenyl	H
	H	4-methoxyphenyl	H
40	H	4-chlorophenyl	H
	H	3,4-dichlorophenyl	H
	H	4-ethoxycarbonylphenyl	H
45	H	H	2,6-dimethylphenyl
	H	H	5-indanyl
50	H	H	4-acetylphenyl
	H	2,6-dimethylphenyl	phenyl
	H	5-indanyl	phenyl
55	H	4-acetylphenyl	phenyl
	H	2,6-dimethylphenyl	H
60	H	5-indanyl	H
	H	4-acetylphenyl	H

Particularly preferred compounds are:

	R ₁	R ₂	R ₃	Code
5	H	H	4-methylphenyl	VIS 130
	H	H	4-methoxyphenyl	VIS 239
	H	H	4-chlorophenyl	VIS 238
10	H	H	3,4-dichlorophenyl	VIS 135
	H	phenyl	phenyl	VIS 046
15	H	4-methoxyphenyl	phenyl	VIS 058
	H	4-chlorophenyl	phenyl	VIS 063
	phenyl	phenyl	phenyl	VIS 040
20	4-methylphenyl	4-methylphenyl	phenyl	VIS 056
	H	phenyl	H	VIS 041
25	H	4-methylphenyl	H	VIS 059
	H	4-methoxyphenyl	H	VIS 067
	H	4-chlorophenyl	H	VIS 066
30	H	H	phenyl	VIS 412
	H	H	4-ethoxycarbonylphenyl	VIS 242
35	H	4-methylphenyl	phenyl	VIS 065
	H	2,6-dimethylphenyl	H	VIS 440
	H	5-indanyl	H	VIS 442
40	H	4-acetylphenyl	H	VIS 073

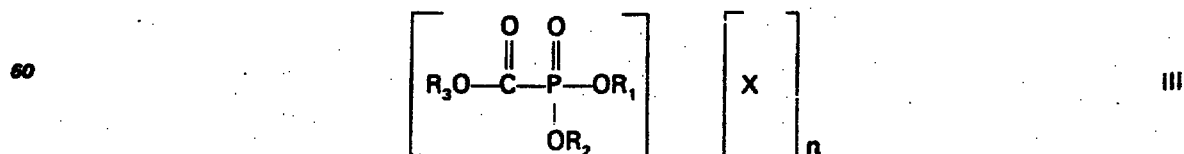
45 and physiologically acceptable salts thereof.

Salts of the active substances

Physiologically acceptable salts of those active substances of the formula I which form salts are prepared by methods known in the art as illustrated in the following.

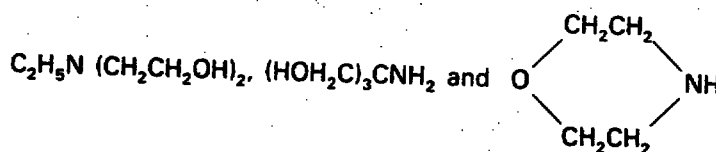
50 Examples of metal salts which can be prepared are salts containing Li, Na, K, Ca, Mg Zn, Mn and Ba. A less soluble metal salt can be precipitated from a solution of a more soluble salt by addition of a suitable metal compound. Thus for examples, Ca, Ba, Zn, Mg, and Mn salts of the active substances can be prepared from sodium salts thereof. The metal ion of a metal salt of the active substances can be exchanged by hydrogen ions, other metal ions, ammonium and ammonium ions substituted by one or
55 more organic radicals by using a cation exchanger.

Examples of other useful salts which can be prepared in this way are the salts of the formula



in which formula R₁, R₂ and R₃ have the same meaning as above, n is 1 or 2, and X is a salt-forming
65 component such as

NH_3 , CH_3NH_2 , $\text{C}_2\text{H}_5\text{NH}_2$, $\text{C}_3\text{H}_7\text{NH}_2$, $\text{C}_4\text{H}_9\text{NH}_2$, $\text{C}_5\text{H}_{11}\text{NH}_2$, $\text{C}_6\text{H}_{13}\text{NH}_2$, $(\text{CH}_3)_2\text{NH}$, $(\text{C}_2\text{H}_5)_2\text{NH}$, $(\text{C}_3\text{H}_7)_2\text{NH}$,
 $(\text{C}_4\text{H}_9)_2\text{NH}$, $(\text{C}_5\text{H}_{11})_2\text{NH}$, $(\text{C}_6\text{H}_{13})_2\text{NH}$, $(\text{CH}_3)_3\text{N}$, $(\text{C}_2\text{H}_5)_3\text{N}$, $(\text{C}_3\text{H}_7)_3\text{N}$, $(\text{C}_4\text{H}_9)_3\text{N}$, $(\text{C}_5\text{H}_{11})_3\text{N}$, $(\text{C}_6\text{H}_{13})_3\text{N}$,
 $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, $\text{HOCH}_2\text{CH}_2\text{NH}_2$, $(\text{HOCH}_2\text{CH}_2)_2\text{NH}$, $(\text{HOCH}_2\text{CH}_2)_3\text{N}$, $\text{C}_2\text{H}_5\text{NH}(\text{CH}_2\text{CH}_2\text{OH})$,



Further examples of other useful salts which can be prepared by the ion exchange technique are quarternary ammonium salts of the active substances, i.e. salts in which the hydrogens in the active substances (structural formula I) have been substituted with quarternary ammonium ions such as $(\text{CH}_3)_4\text{N}$, $(\text{C}_3\text{H}_7)_4\text{N}$, $(\text{C}_4\text{H}_9)_4\text{N}$, $(\text{C}_5\text{H}_{11})_4\text{N}$, $(\text{C}_6\text{H}_{13})_4\text{N}$ and $\text{C}_2\text{H}_5\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3$. Lipophilic salts of this type can also be prepared by mixing a salt of the active substances with a quarternary ammonium salt in water and extracting out the resulting quarternary ammonium salt of the active substances with an organic solvent such as dichloromethane, chloroform, ethyl acetate and methyl isobutyl ketone.

The compounds utilized within the invention may be formulated for use in human and veterinary medicine for therapeutic and prophylactic use. The compounds may be used in the form of a physiologically acceptable salt. Suitable salts are e.g. amine salts, e.g. dimethylamine and triethylamine salt, ammonium salt, tetrabutylammonium salt, cyclohexylamine salt, dicyclohexylamine salt; and metal salts, e.g. mono-, and disodium salt, mono- and dipotassium salt, magnesium salt, calcium salt and zinc salt.

The compounds utilized within the invention are particularly useful for systemic treatment of virus infections, by oral administration or by injection. In comparison with phosphonoformic acid, they are generally more stable in acid solutions, and are thus less readily decomposed in the stomach.

In comparison with phosphonoformic acid the compounds of the present invention are more lipophilic and are thus more suitable to treat virus infections in organs for which penetration through lipid barriers are of importance.

In clinical practice the compound will normally be administered topically, orally, intranasally, by injection or by inhalation in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier which may be a solid, semi-solid or liquid diluent or an ingestible capsule, and such preparations comprise a further aspect of the invention. The compound may also be used without carrier material. As examples of pharmaceutical preparations may be mentioned tablets, drops such as nasal and eye drops, preparations for topical application such as ointments, jellies, creams and suspensions, aerosols for inhalation, nasal spray, liposomes, etc. Usually the active substance will comprise between 0.05 and 99, or between 0.1 and 99% by weight of the preparation, for example between 0.5 and 20% for preparations intended for injection and between 0.1 and 50% for preparations intended for oral administration.

To produce pharmaceutical preparations in the form of dosage units for oral application containing a compound of the invention the active ingredient may be mixed with a solid, pulverulent carrier, for example lactose, saccharose, sorbitol, mannitol, a starch such as potato starch, corn starch, amylopectin, laminaria powder or citrus pulp powder, a cellulose derivative or gelatine and also may include lubricants such as magnesium or calcium stearate or a Carbowax® or other polyethylene glycol waxes and compressed to form tablets or cores for dragées. If dragées are required, the cores may be coated for example with concentrated sugar solutions which may contain gum arabic, talc and/or titanium dioxide, or alternatively with a film forming agent dissolved in easily volatile organic solvents or mixtures of organic solvents. Dyestuffs can be added to these coatings, for example, to distinguish between different contents of active substance. For the preparation of soft gelatine capsules consisting of gelatine and, for example, glycerol as a plasticizer, or similar closed capsules, the active substance may be admixed with a Carbowax® or a suitable oil as e.g. sesam oil, olive oil, or arachis oil. Hard gelatine capsules may contain granulates of the active substance with solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol, starches (for example potato starch, corn starch or amylopectin), cellulose derivatives or gelatine, and may also include magnesium stearate or stearic acid as lubricants.

By using several layers of the active drug, separated by slowly dissolving coatings sustained release tablets are obtained. Another way of preparing sustained release tablets is to divide the dose of the active drug into granules with coatings of different thicknesses and compress the granules into tablets together with the carrier substance. The active substance can also be incorporated in slowly dissolving tablets made for instance of fat and wax substances or evenly distributed in a tablet of an insoluble substance such as a physiologically inert plastic substance.

In order to obtain dosage units of oral preparations — tablets, capsules, etc. — which are

designed so as to prevent release of and possible decomposition of the active substance in the gastric juice, the tablets, dragées etc. may be enteric coated, that is provided with a layer of a gastric juice resistant enteric film or coating having such properties that it is not dissolved at the acidic pH in the gastric juice. Thus, the active substance will not be released until the preparation reaches the intestines.

- 5 As examples of such known enteric coatings may be mentioned cellulose acetate phthalate, hydroxypropylmethylcellulose phthalates such as those sold under the trade names HP 55 and HP 50, and Eudragit®L and Eudragit®S.

- Effervescent powders are prepared by mixing the active ingredient with non-toxic carbonates or hydrogen carbonates of e.g. sodium, potassium or calcium, such as calcium carbonate, potassium carbonate and potassium hydrogen carbonate, solid, non-toxic acids such as tartaric acid, ascorbic acid, and citric acid, and for example aroma.

- Liquid preparations for oral application may be in the form of elixirs, syrups or suspensions, for example solutions containing from about 0.1% to 20% by weight of active substance, sugar and a mixture or ethanol, water, glycerol, propylene glycol and optionally aroma, saccharine and/or carboxy-
15 methylcellulose as a dispersing agent.

For parenteral application by injection preparations may comprise an aqueous suspension of the active compounds according to the invention, desirably in a concentration of 0.5—10%, and optionally also a stabilizing agent and/or buffer substances in aqueous solution. Dosage units of the solution may advantageously be enclosed in ampoules.

- 20 For topical application, especially for the treatment of herpes virus infections on skin, genitals and in mouth and eyes and preparations are suitably in the form of a solution, ointment, gel, suspension, cream or the like. The amount of active substance may vary, for example between 0.05—20% by weight of the preparation. Such preparations for topical application may be prepared in known manner by mixing the active substance with known carrier materials such as isopropanol, glycerol, paraffine, 25 stearyl alcohol, polyethylene glycol, etc. The pharmaceutically acceptable carrier may also include a known chemical absorption promoter. Examples of absorption promoters are e.g. dimethylacetamide (U.S. Patent No. 4,472,931), trichloroethanol or trifluoromethanol (U.S. Patent No. 3,891,757), certain alcohols and mixtures thereof (British Pat. No. 1,001,949). A carrier material for topical application to unbroken skin is also described in the British patent specification No. 1,464,975, which discloses a
30 carrier material consisting of a solvent comprising 40—70% (v/v) isopropanol and 0—60% (v/v) glycerol, the balance, if any, being an inert constituent or a diluent not exceeding 40% of the total volume of solvent.

- The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as for example the severity of the infection, the age of the patient, 35 etc., and may have to be individually adjusted. As a possible range for the amount of the active substance which may be administered per day may be mentioned from about 0.1 mg to about 2000 mg or from about 1 mg to about 2000 mg, or preferably from 1 mg to about 2000 mg for topical administration, from 50 mg to about 2000 mg or from 100 to 1000 mg for oral administration and from 10 mg to about 2000 mg or from 50 to 500 mg for injection. In severe cases it may be necessary
40 to increase these doses 5-fold to 10-fold. In less severe cases it may be sufficient to use up to 500 or 1000 mg.

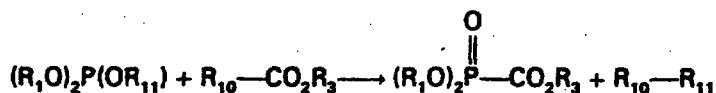
The pharmaceutical compositions containing the active ingredients may suitably be formulated so that they provide doses within these ranges either as single dosage units or as multiple dosage units and are preferably provided as sterile preparations.

- 45 Thus, it has been found according to the invention that the above compounds, and the physiologically acceptable salts thereof can be used to selectively inhibit the multiplication of viruses and the compounds and physiologically acceptable salts thereof are therefore useful in therapeutic and/or prophylactic treatment of virus infections and neoplastic diseases, as described above.

- The hydroxycarbonylphosphonic acid triesters may be prepared by known methods for example as 50 described in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII, Teil 1, Organische Phosphorverbindungen, s. 433—463. Examples of such methods are the following.

Reference to "meaning given above" for R_1 , R_2 and R_3 as used below refers to the definitions given in formula I.

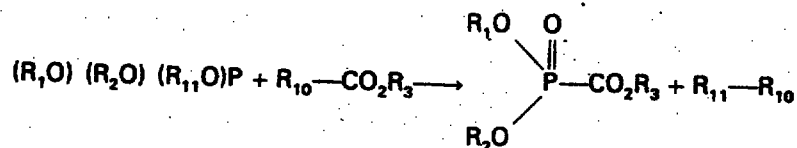
- 55 A. Reacting formic acid ester compounds with phosphite triesters according to the formula:



- 60 wherein R_1 and R_2 have the meaning given above, R_{10} is a leaving group suitable for Arbuzow type reactions, such as for example Cl, Br, I, sulphonate, carboxylate, alkoxide, R_{11} may be an alkyl, a cycloalkyl, a cycloalkyl-alkyl, a benzyl, an adamantyl or any phosphite esterifying group suitable for Arbuzow type reactions.

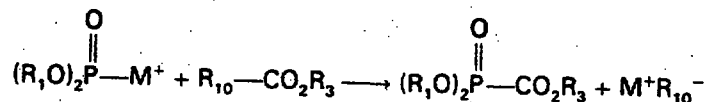
- 65 Preferably the reaction is performed at 0 to 150°C for 1 to 50 hours.

B. Reacting formic acid ester compounds with phosphite triesters according to the formula:



wherein R_1 , R_2 , R_3 , R_{10} and R_{11} have the meaning given above.

C. Reacting formic acid ester compounds with phosphite diester salts according to the formula:

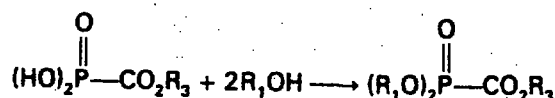


wherein R_1 , R_3 and R_{10} have the meaning given above and M^+ is a cation, preferably a metal such as Li^+ , Na^+ or K^+ , and the reaction is preferably performed at 0 to 100°C for 1 to 50 hours in a solvent such as for example, toluene, ether or tetrahydrofuran.

The phosphite diester salts are prepared by treating the phosphite diester with a suitable proton abstracting compound, such as a metal alkoxide, suitable free from alcohol, such as lithium-, sodium- or potassium methoxide, ethoxide or t-butoxide or with a hydride such as sodium- or potassium hydride, or with a base such as butyllithium.

The starting materials used in the above methods of preparation A—C are known compounds, or may be prepared by known methods commonly used for the synthesis of formate esters and phosphite triesters. Example of methods used for the synthesis of haloformate esters may be found in, or referred to in M. Matzner et al. Chem. Rev. 64 (1964), 645. Examples of methods used for the synthesis of phosphite triesters may be found in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII, Teil 2, Organische Phosphorverbindungen, p. 5—78.

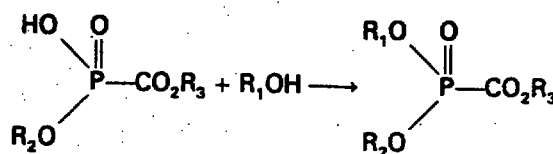
D. Esterification of the phosphonic acid groups of hydroxycarbonylphosphonic acid monoester according to the formula:



R_1 and R_3 have the meaning given above. The reaction is performed through the intermediary of activating agents known *per se* for the phosphorylation of alcohols and phenols. Examples of such methods are described for example by L. A. Slotin in Synthesis 1977, 737 and by H. Seliger and H. Kössel in Progress in the Chemistry of Organic Natural Products 32 (1975) 297.

Synthesis of monoesters of the carboxylic group of hydroxycarbonylphosphonic acid are described below in methods S—W.

E. Esterification of hydroxycarbonylphosphonic acid diesters according to the formula:

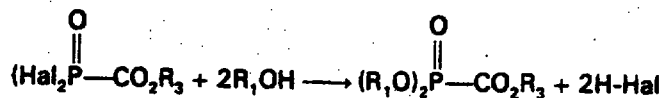


R_1 , R_2 and R_3 have the meaning given above.

The reaction is performed through the intermediary of activating agents known *per se* for the phosphorylation of alcohols and phenols. Examples of such methods are described for example by L. A. Slotin in Synthesis 1977, 737, and by H. Seliger and H. Kössel in Progress in the Chemistry of Organic Natural Products 32 (1975) 297.

Synthesis of hydroxycarbonylphosphonic acid diesters are described below in methods J—N.

F. Reacting hydroxycarbonylphosphonic acid dihalide esters according to the formula:



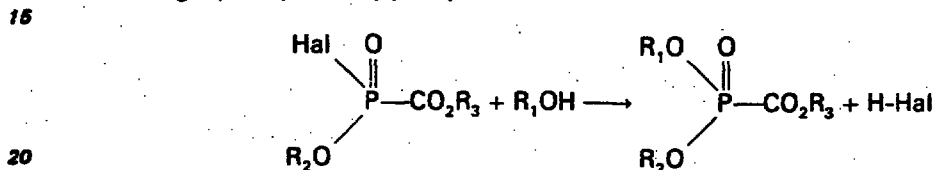
Hal is Cl, Br or I and R_1 and R_2 have the meaning given above.

The reactions are performed by methods known *per se* for the phosphorylation of alcohols and phenols by phosphoric and phosphonic acid halides. Examples of such methods are described for example by L. A. Slotin in *Synthesis* 1977, 737 and by H. Seliger and H. Kössel in *Progress in the Chemistry of Organic Natural Products* 32 (1975) 297.

The hydroxycarbonylphosphonic acid dihalide esters are prepared from hydroxycarbonylphosphonic acid monocarboxylic esters by methods known *per se* for the synthesis of dihalides of phosphonic acids and phosphoric acids. References for those methods are found for example in the two publications above and in Houben-Weyl, *Methoden der Organischen Chemie*, Auflage 4, Band XII/1 S. 386—406 and Band XII/2 S. 211—225 and S. 274—292.

Hydroxycarbonylphosphonic acid monocarboxylic esters are prepared by methods described below in S—W.

G. Reacting hydroxycarbonylphosphonic acid monohalide diesters according to the formula:



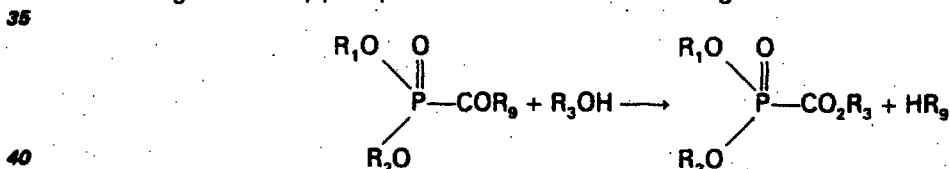
Hal is Cl, Br, or I and R_1 , R_2 and R_3 have the meaning given above.

The reaction is performed by methods known *per se* for the phosphorylation of alcohols and phenols. Examples of such methods are described for example by L. A. Slotin in *Synthesis* 1977, 737 and by H. Seliger and H. Kössel in *Progress in the Chemistry of Organic Natural Products* 32 (1975) 297.

Hydroxycarbonylphosphonic acid monohalide diesters are prepared from hydroxycarbonylphosphonic acid diesters by methods known *per se* for the synthesis of monohalides of phosphonic and phosphoric acids. References for those methods are found for example in the two publications above and in Houben-Weyl, *Methoden der organischen Chemie*, Auflage 4, Band XII/1, s. 386—406 and Band XII/2 s. 211—225 and s. 274—292.

Hydroxycarbonylphosphonic acid diesters are prepared by methods described below in J—N.

H. Reacting a carbonylphosphonic acid diester according to the formula:

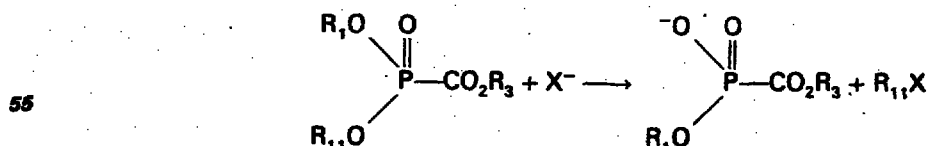


R_1 , R_2 and R_3 have the meaning given above and R_9 is a suitable activating moiety, known *per se* as a good leaving group in substitution reactions on activated carboxylic acid groups. Preferably R_9 is a group such as for example p-nitrophenoxy or imidazolyl.

The activated carbonylphosphonic acid diesters used as a starting material may for example be prepared by methods analogous to those described above in A—C.

Diesters of hydroxycarbonylphosphonic acid are prepared by known methods, such as

J. Reacting a hydroxycarbonylphosphonic acid triester with an iodide or a bromide anion, according to the formula:

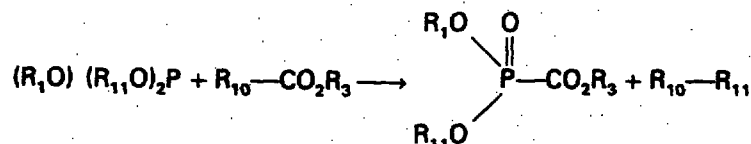


wherein X is Br or I and R_1 , R_3 and R_{11} have the meaning given above.

Preferably the reaction is carried out with sodium iodide in a solvent such as for example tetrahydrofuran or acetone. Preferably the reaction is carried out at a temperature from 20 to 100°C from 2 hours to 7 days.

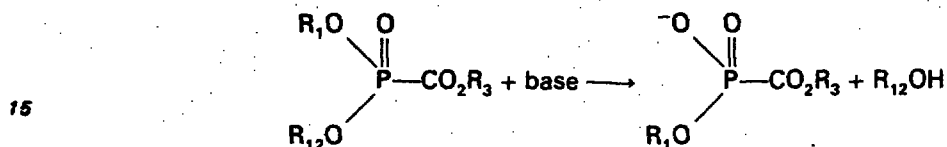
The hydroxycarbonylphosphonic acid triester may be prepared by methods analogous to those described above in A—H.

A similar reaction to obtain the triester, is the following reaction between a phosphite triester and a formic acid ester:



wherein R_1 , R_3 , R_{10} and R_{11} have the meaning given above. Preferably the reaction is performed at 20 to 100°C from 2 hours to 7 days.

10 K. Hydrolysing a hydroxycarbonylphosphonic acid triester with a base according to the formula:

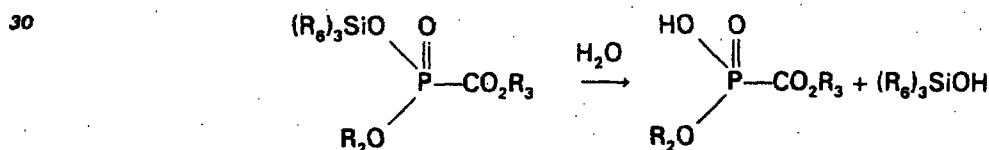


R_1 and R_3 have the meaning given above. R_{12} is a hydrolyzable phosphate ester group. For example it may have the meaning given R_1 and R_2 and it may for example be a more generally substituted aryl group, benzyl or a suitable alkyl group.

Preferably the reaction is carried out with a base such as for example sodium hydrogencarbonate, sodium carbonate or sodium hydroxide in water at a temperature from 20 to 100°C from 2 hours to 7 days.

The hydroxycarbonylphosphonic acid triester may be prepared by methods analogous to those described above in A—J.

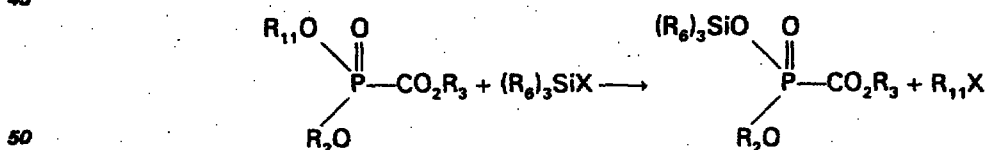
L. Aqueous hydrolysis of a hydroxycarbonyl phosphonic acid triester, containing one silyl esterified phosphonate group according to the formula:



where R_2 and R_3 have the meaning given above and R_6 is an inert organic residue, preferably an organic group such as for example CH_3 . Another example of silyl ester groups are for example butyldiphenylsilyl compounds, which have been described by R. A. Jones et al. Biochemistry 17 (1978) 1268 as phosphate ester derivatives.

Optionally the formed phosphonic acid group may be neutralized with a base such as for example $MHCO_3$, M_2CO_3 or MOH or with a weak cation exchanger (M^+), where M^+ is NH_4^+ or a metal such Li^+ , Na^+ or K^+ .

The silyl esterified phosphonate group may be obtained by treating the hydroxycarbonyl phosphonic acid triester with a halosilane according to the formula:

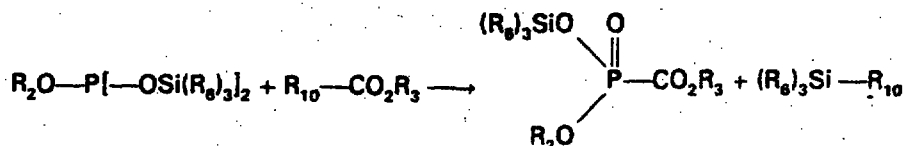


X is Cl, Br or I and R_2 , R_3 , R_6 and R_{11} have the meaning given above.

Preferably the reagents used for silylation are for example bromotrimethylsilane at -20° to 50°C for 1/2 to 20 hours, or alternatively for example chlorotrimethylsilane at 20° to reflux temperature for several days.

The hydroxycarbonylphosphonic acid triesters are prepared by methods analogous to those described above in A—J.

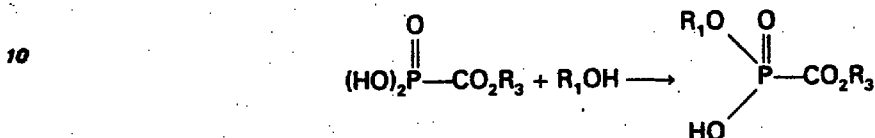
Alternatively the compound containing the silyl esterified phosphonate group may be prepared by reacting a phosphite triester containing two silyl ester groups, with a formate ester, according to the formula:



R_2 , R_3 , R_6 and R_{10} have the meaning given above.

Preferably the phosphite is an ester such as for example a bis-(trimethylsilylated) phosphite triester. These compounds can be prepared by methods known *per se*. For example the synthesis of propyl- and hexyl-bis-(trimethylsilyl)phosphites are described in T. R. Herrin et al., J. Med. Chem. 20 (1977) 660.

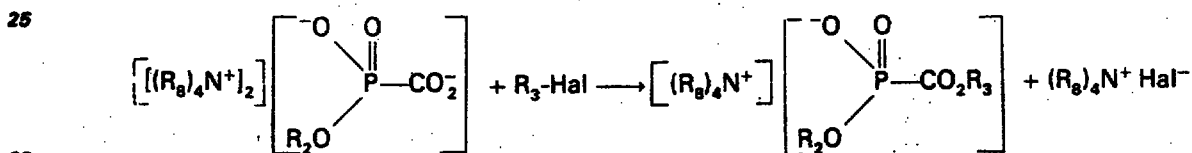
M. Reacting hydroxycarbonylphosphonic acid monocarboxylic esters according to the formula:



R_1 and R_3 have the meaning given above. The reaction is performed through the intermediary of activating agents known *per se* for the phosphorylation of alcohols and phenols. Examples of such methods are described for example by L. A. Slotin in Synthesis 1977, 737 and by H. Seliger and H. Kössel in Progress in the Chemistry of Organic Natural Products 32 (1975) 297.

Synthesis of hydroxycarbonylphosphonic acid monocarboxylic acids are described below in methods S—W.

N. Reacting hydroxycarbonylphosphonic acid mono-P ester with an esterifying halide, using a tetra-alkylammoniumsalt as a catalyst, according to the formula:



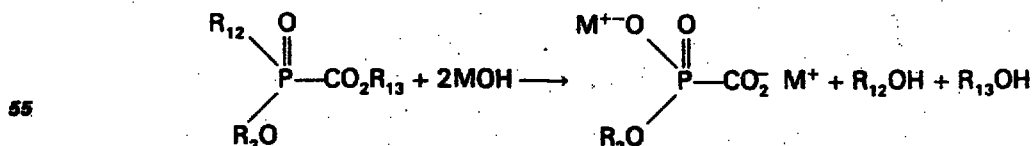
Hal is Cl, Br or I. R_2 and R_3 have the meaning given above and R_8 is an alkyl residue such as for example n-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl. Preferably n-heptyl is used and preferably the reaction is performed as an extractive alkylation as described by for example A. Brändström in Preparative Ion Pair Extraction (Apotekarsocieteten, Håssle, Sweden 1976). Also as described the phosphate group may be transformed to a salt



where M^+ is for example NH_4^+ or a metal such as Li^+ , Na^+ or K^+ .
The synthesis of hydroxycarbonylphosphonic acid mono-P esters are described below in methods O—R.

Monoesters of the phosphonic acid group of hydroxycarbonylphosphonic acid are prepared by known methods such as,

O. Hydrolyzing a hydroxycarbonylphosphonic acid triester according to the formula:

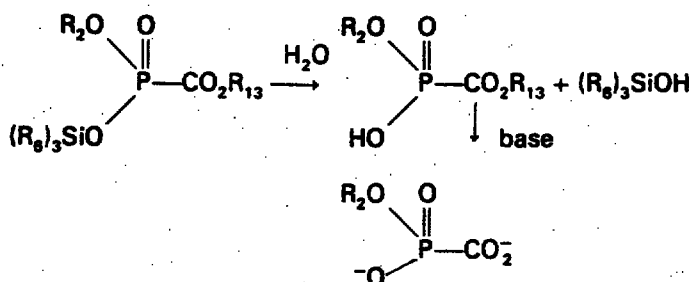


wherein M is a cation such as NH_4^+ or Li^+ , Na^+ or K^+ and wherein R_2 and R_{12} have the meaning given above. R_{13} has the meaning given R_{12} , and R_{12} and R_{13} may be the same or different.

Preferably the reaction is carried out in water at 20 to 100°C for 1 to 10 hours.

The hydroxycarbonylphosphonic acid triesters are prepared by methods analogous to those described above in A—J.

P. By the stepwise deesterification of a phosphonic acid trisubstituted silyl ester group, and the carboxylic acid ester group, of hydroxycarbonylphosphonic acid triesters, according to the formula:



R₂, R₆ and R₁₃ have the meaning given above, and the silyl ester group is preferably a group such as exemplified above in method L.

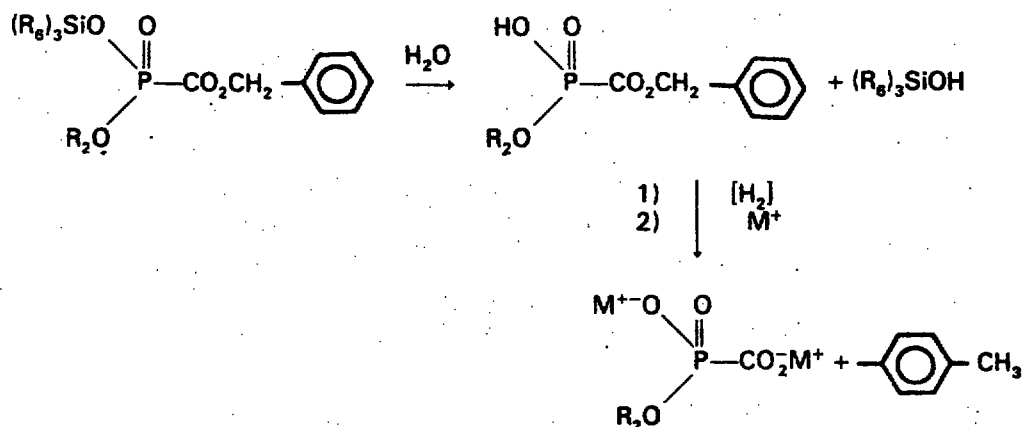
The trimethyl silyl ester group is preferably hydrolyzed with water and the free acid group is preferably converted to a salt by a weak cation exchanger (M⁺) or with an aqueous base such as MHCO₃, M₂CO₃ or MOH.

The carboxylic acid ester group is preferably hydrolyzed in for example water and neutralized with a weak cation exchanger (M⁺) or with for example an aqueous base such as MHCO₃, M₂CO₃ or MOH.

M⁺ is NH₄⁺ or a metal such as Li, Na, or K.

Compounds containing the silylesterified phosphonate group may be prepared by known methods as described in method L above.

Q. By the stepwise deesterification of the silyl and benzyl ester group of aryl silyl benzyloxycarbonylphosphonate according to the formula:

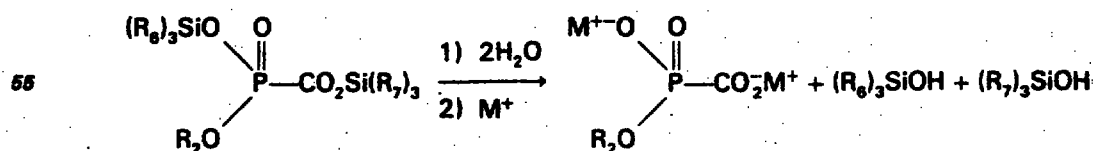


M⁺ is NH₄⁺ or a metal such as for example Li⁺, Na⁺ or K⁺, and R₂ and R₆ have the meaning given above. The silyl ester group is preferably a group such as described above in method L.

The benzyl ester group is preferably hydrogenated with a catalyst such as for example palladium carbon. The free acid groups are converted to their metal salts by the treatment with a weak cation exchanger (M⁺) or with a base such as for example MHCO₃, M₂CO₃ or MOH.

The silylated compound may be prepared by known methods, analogous to those described above in L.

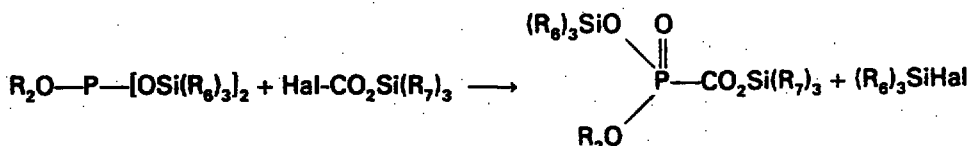
R. By the deesterification of the bis-silylester groups (on the phosphonic and on the carboxylic acid groups) of hydroxycarbonylphosphonic acid triesters according to the formula:



R₂ has the meaning given above, R₆ and R₇ are inert organic residues, the same or different, preferably they are the same and a group such as for example CH₃. The silyl ester groups may also be for example butyldiphenylsilyl groups as described above in method L. M⁺ is NH₄⁺ or a metal such as Li⁺, Na⁺ or K⁺.

The silyl ester groups are preferably hydrolyzed with for example water and neutralized with for example a weak cation exchanger (M⁺) or an aqueous base such as MHCO₃, M₂CO₃ or MOH.

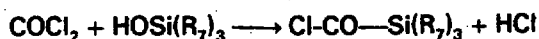
The bis-silylated triester of hydroxycarbonylphosphonic acid may be prepared by methods known per se, according to the formula:



Hal is Cl, Br or I, and R_2 , R_6 and R_7 have the meaning given above.

Preferably the phosphite is an ester such as for example a bis(trimethylsilylated) phosphite triester. These compounds can be prepared as described above in L.

The haloformate silylesters may be prepared according to the formula:

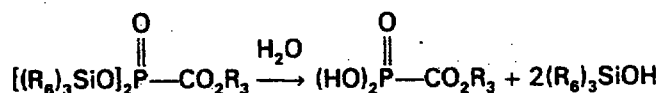


R_7 has the meaning given above.

The reaction is carried out under anhydrous conditions, and preferably a base such as for example N,N-dimethylaniline is used for capturing the released hydrogen chloride. The reaction is preferably carried out in an inert solvent such as for example toluene or ether, at for example -10 to $25^\circ C$ for 1 to 25 hours.

Monoesters of the carboxylic group of hydroxycarbonylphosphonic acid are prepared by known methods, such as

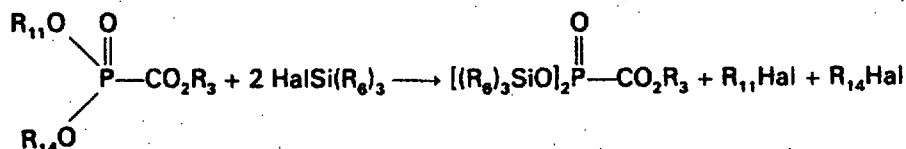
S. Aqueous hydrolysis of a hydroxycarbonylphosphonic acid triester, containing two silyl esterified phosphonate groups, according to the formula:



R_3 and R_6 have the meaning given above. Preferably R_6 is for example CH_3 . The silyl ester derivatives may also be for example butyldiphenylsilyl groups as described above in method L.

Optionally the formed phosphonic acid groups can be neutralized. Preferably they may be neutralized with a weak cation exchanger (M^+) or with base such as $MHCO_3$, M_2CO_3 or MOH . M^+ is NH_4^+ or a metal such as Li^+ , Na^+ or K^+ .

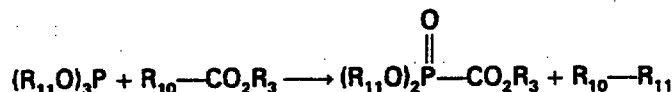
The phosphonate bis-silyl esters may be obtained according to the formula:



R_3 , R_6 and R_{11} have the meaning given above. R_{14} has the meaning given R_{11} , and R_{11} and R_{14} may be the same or different. Preferably the organic residues of the silyl group are as described above. Hal is Cl, Br or I and preferably the reaction is performed at $-20^\circ C$ to reflux temperature for 1 hour to several days.

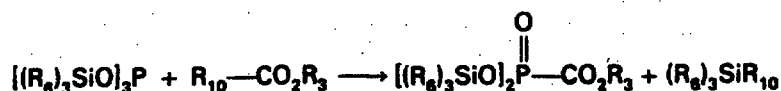
The hydroxycarbonylphosphonic acid triesters are prepared by methods analogous to those described above in A—J.

Another similar way of obtaining the hydroxycarbonylphosphonic acid triester is the reaction according to the following formula:



wherein R_3 , R_{10} and R_{11} have the meaning given above.

Alternatively the bis-silylphosphonate esters may be prepared by reacting a tris-silylphosphite with a formate ester according to the formula:

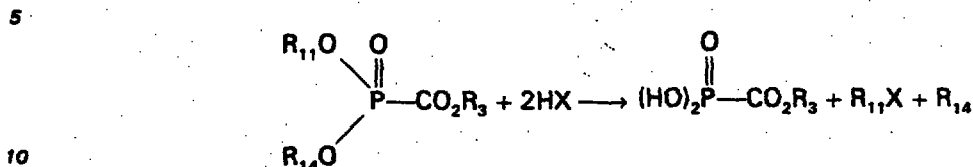


R_3 , R_6 and R_{10} have the meaning given above and preferentially the organic residues of the silyl group are as described above. Preferably the reaction is performed at $20-150^\circ C$ for 1 to 25 hours.

The tris-silylphosphites are prepared by known methods, as described for example by Herrin et al

in J. Med. Chem. 20 (1977) 880, for the preparation of tris(trimethylsilyl)phosphite.

T. Reacting triesters of hydroxycarbonylphosphonic acid with hydrohalide acids according to the formula:



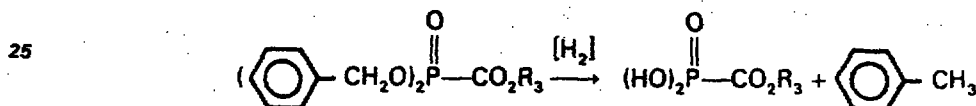
R_3 , R_{11} and R_{14} have the meaning given above. X is Cl, Br or I.

Preferably HI may be used and the reaction may preferably be performed in a dry solvent such as methylene chloride or acetic acid at a temperature from 0 to 30°C. Examples of the reaction may be found in the patents USP 3 943 201 and DT-OLS 2435 407.

Optionally the phosphonic acid groups may be neutralized. Preferably a weak cation exchanger (M^+) or a base such as MHCO_3 , M_2CO_3 or MOH is used. M^+ is for example NH_4^+ or a metal such as Li^+ , Na^+ or K^+ .

The hydroxycarbonylphosphonic acid triester may be prepared by methods analogous to those described above in A—J and S.

U. Hydrogenating dibenzyl, aryloxyphosphonates according to the formula:



R_3 has the meaning given above.

Preferably the reaction may be performed with a catalyst such as palladium carbon. Optionally the phosphonic acid groups may be neutralized. Preferably they may be neutralized with a weak cation exchanger (M^+) or with a base such as MHCO_3 , M_2CO_3 or MOH , M^+ is for example NH_4^+ or a metal such as Li^+ , Na^+ or K^+ .

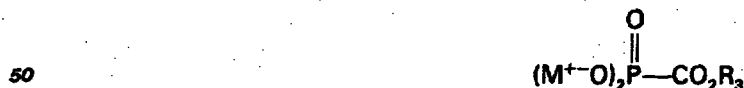
The hydroxycarbonylphosphonic acid triesters may be prepared by methods analogous to those described above in A—J and S.

V. Reacting hydroxycarbonylphosphonic acid with an esterifying halide, using a tetraalkylammonium salt as a catalyst, according to the formula



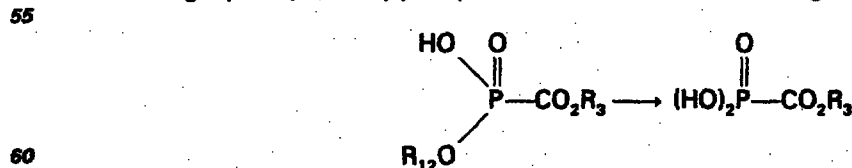
Hal is Cl, Br or I. R_3 has the meaning given above and R_8 is an alkyl residue, such as for example n-butyl, n-pentyl, n-hexyl, n-heptyl and N-octyl. Preferably n-heptyl is used and preferably the reaction is performed as an extractive alkylation, as described by for example A. Brändström, Preparative Ion Pair Extraction (Apotekarsocieteten, Håssle; Sweden (1976)).

Also as described, the phosphonate groups may be transformed to a disalt



where M^+ is for example NH_4^+ or a metal such as Li^+ , Na^+ or K^+ .

W. Reacting hydroxycarbonylphosphonic acid diesters according to the formula:



R_3 and R_{12} have the meaning described above.

The preparations may be performed by procedures analogous to those described above in S—U.

Optionally the monocarboxylic ester thus obtained may be neutralized with a weak cation

exchanger or with a base such as MHCO_3 , M_2CO_3 or MOH , M^+ is for example NH_4^+ or a metal such as Li^+ , Na^+ or K^+ .

The oxycarbonylphosphonic acid diesters may be prepared by methods described above in J—N. Preparation of triesters of hydroxycarbonylphosphonic acid.

Example 1

Hydroxycarbonylphosphonic acid triphenyl ester

7.87 g (0.03 mole) of ethyl diphenylphosphite (B. F. Griffin and A. Burger, J. Amer. Chem. Soc. 78 (1956) 2336) and 9.39 g (0.06 mole) of freshly distilled phenyl chloroformate were heated at 110° overnight. Volatile components were evaporated *in vacuo* to give 10.5 g (98%) of the title compound as a residue. Analysis by gas liquid chromatography (Perkin-Elmer column OV 17, 250°C) shows a practically pure compound (> 95%). NMR (CDCl_3) δ : 6.90—7.33 (multiplet).

Example 2

Di-p-tolyl phenoxycarbonylphosphonate

29.0 g (0.1 mole) of ethyl di-p-tolylphosphite and 31.3 g (0.2 mole) of phenyl chloroformate were heated at 110° overnight. Volatile components were evaporated *in vacuo* (0.3 mm) at 110° to give the title compound as a residue. n_D^{25} 1.5554 NMR (CDCl_3) δ : 2.30 (s, CH_3), 6.9—7.6 (m, aryl). IR (neat) cm^{-1} : 1740 (CO), 1590, 1510, 1300, 1190, 1160, 970.

An example of methods used for the synthesis of triesters of phosphorous acid.

Example 3

Ethyl di-p-tolylphosphite

The synthesis was carried out by the method described by B. S. Griffin and A. Burger JACS 78 (1956) 2336 for the preparation of ethyl diphenylphosphite. A solution of 103.85 g (0.37 mole) di-p-tolyl phosphorochloridite in 175 ml of dry hexane was added with stirring and over a period of four hours to an ice-cold solution of 29.27 g (0.37 mol) of pyridine and 18.00 g (0.39 mole) of absolute ethanol in 175 ml of dry hexane. The mixture was stirred at room temperature overnight. The pyridinium chloride was filtered off and was washed with dry hexane. The solvent was removed *in vacuo* (15 mm) on a rotavapor. The residual oil was fractionated by distillation *in vacuo*. The fraction boiling at 138—165°C 0.03 mm was collected to yield 74.5 g of a colourless oil (69%). n_D^{25} 1.5382. Analysis for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{P}$. Found (Calculated): C 65.61 (66.20), H 6.48 (6.20), P 10.47 (10.67). NMR (CDCl_3) δ : 1.27 (t, J 7Hz, CH_3), 2.20 (s, Ar- CH_3), 4.20 (quintet, J 7Hz, CH_2), 7.02 (s, aryl). IR (neat) cm^{-1} : 2980, 1610, 1510, 1200, 1170, 1030, 950.

Preparation of diesters of hydroxycarbonylphosphonic acid.

Example 4

Sodium phenyl phenoxycarbonylphosphonate

10.7 g (0.03 mole) or hydroxycarbonylphosphonic acid triphenyl ester and 50 g (wet weight, 0.09 mole of Amberlite® IRC 50 (Na^+) were stirred in 100 ml of water, at room temperature overnight. Ethanol was added and the solution was filtered and evaporated *in vacuo*. The residue was redissolved in 25 ml of hot ethanol, filtered and precipitated by the addition of 300 ml of ether. The precipitate (5.11 g) was recrystallized twice from i-propanol to give 3.20 g (35%) of the title compound. Analysis for $\text{C}_{13}\text{H}_{10}\text{NaO}_5\text{P}$. Found (calculated): Na 7.8 (7.7). Molecular weight by titration: 305.1 (300.2).

Example 5

Sodium phenyl phenoxycarbonylphosphonate

3.54 g (10 mmole) of hydroxycarbonylphosphonic acid triphenyl ester and 0.80 g (9.5 mmole) of sodium hydrogen carbonate in 10 ml of water were stirred at room temperature overnight. The solvent was evaporated *in vacuo*, the residue was extracted with 50 ml of ethanol and the ethanol solution was filtered and evaporated. Yield 2.20 g. T.l.c. (silica gel, ethanol) R_f 0.74 Analysis for $\text{C}_{13}\text{H}_{10}\text{NaO}_5\text{P}$. Found (calculated): 8.2 (7.7). The compound was recrystallized twice from i-propanol to give 0.31 g (10%) of the title compound. T.l.c. (silica gel, ethanol): R_f 0.73 (single spot). By t.l.c. (polyethyleneimine, 1M LiOI, molybdate spray) the compound was shown to contain < 0.5% of trisodium oxycarbonylphosphate. Analysis for $\text{C}_{13}\text{H}_{10}\text{NaO}_5\text{P}$. Found (calculated): Na 7.9 (7.7). Molecular weight by titration: 297 (300.2).

Example 6

Similar to the description in example 5, sodium p-tolyl phenoxycarbonylphosphonate was also obtained

From di-p-tolyl phenoxycarbonylphosphonate yield 26%. T.l.c. (silica gel, ethanol): R_f 0.61 single spot. By t.l.c. (polyethyleneimine, 1M LiCl, molybdate spray) the compound was shown to contain < 0.4% of trisodium oxycarbonylphosphonate. $\text{C}_{14}\text{H}_{12}\text{NaO}_5\text{P}$: Found (calculated): C 52.42 (53.52), H 3.95 (3.85), Na 7.38 (7.32) P 10.10 (9.86).

Example 7

Sodium p-methoxyphenyl phenoxycarbonylphosphonate

13.7 g (41 mmole) of ethyl p-methoxyphenyl phenoxycarbonylphosphonate and 12.5 g (82 mmole) of bromotrimethylsilane were stirred under an atmosphere of argon at room temperature overnight. Volatile components were evaporated *in vacuo* (0.3 mm). The residue was added dropwise over a period of 10 min, to a cation exchanger, (IRC Na⁺, 68 g wet, 120 mekv) in 150 ml of water. The mixture was stirred overnight. The ion exchanger was filtered off and was washed with water and ethanol. The solvent was evaporated *in vacuo* and the residue was mixed with 100 ml of water and was extracted with 2 x 50 ml of ether. The water phase was evaporated at reduced pressure (0.3 mm). The residue was treated with 250 ml of absolute boiling ethanol and the mixture was filtered while still hot. 1.30 g of crystalline material was filtered off. The ethanol was evaporated and the residue was dissolved in 50 ml of absolute ethanol. Dry ether was added to precipitate crude sodium p-methoxyphenyl phenoxycarbonylphosphonate 8.82 g, which was recrystallized from i-propanol to give 5.44 g. It was further purified on a column of silica gel eluted with ethanol and finally recrystallized twice from i-propanol to give 3.65 g (27%) of sodium p-methoxyphenyl phenoxycarbonylphosphonate. Analysis for C₁₄H₁₂NaO₆P. Found (calculated): Na 7.2 (7.0), molecular weight by titration 323 (330). T.l.c. (silica gel, ethanol, sprayed consecutively with molybdate and aqueous SnCl₂ with drying inbetween): R_f 0.51 single spot. By t.l.c. (polyethyleneimine, 1M LiCl, molybdate spray) the compound was estimated to contain < 0.2% of trisodium oxycarbonylphosphonate. IR (KBr)cm⁻¹: 1710 (CO), 1510, 1270, 1090, 910.

Example 8

Similar to the description in example 7, sodium p-chlorophenyl phenoxycarbonylphosphonate was prepared and analysed

From ethyl p-chlorophenyl phenoxycarbonylphosphonate. Yield 36%. T.l.c. R_f 0.54 single spot. By t.l.c. the compound was estimated to contain < 0.2% of trisodium oxycarbonylphosphonate. IR(KBr)cm⁻¹: 1710 (CO), 1490, 1270, 1090, 910. Preparation of monoesters of hydroxycarbonylphosphonic acid (of the phosphonic acid group).

Example 9

Phenyl disodium oxycarbonylphosphonate

3.06 g (10 mmole) of diphenyl ethoxycarbonylphosphonate and 19.0 ml of 1.05 N NaOH were heated at reflux for 1 hour. The solution was evaporated *in vacuo* and the product was redissolved in H₂O. The product precipitated with methanol (1.54 g). It was contaminated with some trisodium oxycarbonylphosphonate. It was redissolved in water (10 ml) and ethanol was added until about 1/10 of the total amount had precipitated. This was discarded by filtration. Ethanol was added to the solution and the precipitate was collected and underwent the same selective precipitation procedure once more to give 0.80 g (32%) of phenyl disodium oxycarbonylphosphonate. Analysis for C₇H₅Na₂O₅P. Found (calculated): C 33.91 (34.17), H 1.88 (2.05), Na 18.63 (18.68), P 12.63 (12.59). Equivalent weight by titration: 124.4 (123.0). By t.l.c. (polyethyleneimine, 1M LiCl, molybdate spray) the compound was shown to contain < 0.5% of trisodium oxycarbonylphosphonate.

Example 10.

Analogous to the description in example 9, p-tolyl disodium oxycarbonylphosphonate was prepared From 11.47 g (30 mmole) di-p-tolyl phenoxycarbonylphosphonate (0°C 1 hour, room temperature, overnight, nitrogen atmosphere). Yield 6.51 g (83%) T.l.c. polyethyleneimine, 1M LiCl, molybdate spray) R_f 0.51 single spot. By t.l.c. the compound was estimated to contain < 0.4% of trisodium oxycarbonylphosphonate. Analysis for C₉H₉Na₂O₅P. Found (calculated): C 36.77 (36.94), H 2.71 (2.71), P 11.87 (11.91), Na 17.60 (17.68). NMR (D₂) δ: 4.61 (s, CH₃), 6.90—7.28 (C₆H₄). IR (KBr)cm⁻¹: 1610, 1590, 1220, 1080, 910.

Example 11

p-Methoxyphenyl disodium oxycarbonylphosphonate

16.8 g (50 mmole) of ethyl p-methoxyphenyl phenoxycarbonylphosphonate was stirred under an atmosphere of argon with 12.5 ml (82 mmole) of bromotrimethylsilane for 5 hours. Excess of bromotrimethylsilane was evaporated *in vacuo* (0.03 mm). The mixture was added dropwise to 100 ml of 1.00 M NaOH (0.10 mole) during 10 minutes. The stirring was continued at room temperature during 4 hours. the mixture was extracted with 3 x 75 ml of ether. The water phase was evaporated *in vacuo* and the residue was dissolved in 50 ml of water. The crude disodium p-methoxyphenyl oxycarbonylphosphonate was precipitated with 500 ml of ethanol. Yield 12.1 g. It was contaminated with some trisodium oxycarbonylphosphonate. It was redissolved in water (50 ml) and ethanol (70 ml) was added slowly. The small amount of precipitate was discarded by filtration. Ethanol, 400 ml, was added to the solution and the new precipitate was collected: yield 11.1 g. Analysis for C₈H₇Na₂O₆P. Found (calculated): Na 17.5% (16.65). For further purification it was precipitated with ethanol from a water solution two more times. Yield 8.3 g (60%). T.l.c. (polyethyleneimine, 1M LiCl, molybdate spray): R_f

0.57, single spot. By t.l.c. (the same system) the compound was estimated to contain < 0.4% of trisodium oxycarbonylphosphonate. Analysis for $C_8H_7Na_2O_6P$. Found (calculated): C 34.94 (34.80), H 2.55 (2.56), Na 16.82 (16.65), P 11.38 (11.22). IR (KBr) cm^{-1} : 1590, 1510, 1240, 1210, 1080, 900.

Example 12

Analogous to the description in example 11, the following compounds were prepared and analysed.

a) *p*-Chlorophenyl disodium oxycarbonylphosphonate

From ethyl *p*-chlorophenyl phenoxycarbonylphosphonate. Yield 64% after the first precipitation from water with ethanol. Further purification by repeated precipitations gave a yield of 32%. T.l.c. R_f 0.51, single spot. By t.l.c. the compound was estimated to contain < 0.4% of trisodium oxycarbonylphosphonate. IR (KBr) cm^{-1} : 1590, 1490, 1240, 1220, 1080, 900.

b) 2,6-Dimethylphenyl disodium oxycarbonylphosphonate

From ethyl 2,6-dimethylphenyl methoxycarbonylphosphonate. Yield 78%. T.l.c. R_f 0.56, single spot. By t.l.c. the compound was estimated to contain < 0.4% of trisodium oxycarbonylphosphonate. NMR (D_2O) δ : 2.30 (s, CH_3), 7.07—7.27 (C_6H_3). IR (KBr) cm^{-1} : 1610 (CO), 1490, 1390, 1230, 1200, 1100, 1080, 930.

c) 5-Indanyl disodium oxycarbonylphosphonate

From ethyl 5-indanyl methoxycarbonylphosphonate. Yield 72%. T.l.c. R_f 0.39, single spot. By t.l.c. the compound was estimated to contain < 0.4% of trisodium oxycarbonylphosphonate. Analysis for $C_{10}H_9O_5PNa_2 \times H_2O$. Found (calculated): C 39.29 (39.42), H 3.20 (3.65), Na 16.8 (15.1), H_2O 6.4 (5.9). NMR (D_2O) δ : 1.8—2.3 (CH_2), 2.7—3.0 (CH_2-C-CH_2), 6.9—7.3 (C_6H_3). IR (KBr) cm^{-1} : 1600 (CO), 1500, 1480, 1250, 1230, 1090, 970.

d) 4-Acetylphenyl disodium oxycarbonylphosphonate

From 6.0 g (16 mmole) of methyl *p*-acetylphenyl *p*-nitrophenoxycarbonylphosphonate and 3.05 g (20 mmole) of bromotrimethylsilane. After the reaction excess of bromotrimethylsilane was evaporated *in vacuo* and the residue was added to 30 g (about 50 meq) of Amberlite IRC 50 (Na^+) in 50 ml of H_2O and stirred at room temperature. The solution was filtered, washed with ether and centrifuged. The water solution was treated with activated carbon and filtered. By repeated precipitations from water solutions with ethanol, 5-acetylphenyl disodium oxycarbonylphosphonate was obtained. T.l.c. R_f 0.56. By t.l.c. the compound was estimated to contain 5—10% of trisodium oxycarbonylphosphonate. NMR (D_2O) δ : 2.67 (s, CH_3), 7.32 and 8.05 (doublets, J 9Hz, C_6H_4). IR (KBr) cm^{-1} : 1590, 1370, 1240, 1080 900.

Examples of methods for the preparation of monoesters of the carboxylic group of hydroxycarbonylphosphonic acid.

Example 13.

Disodium phenoxycarbonylphosphonate

1.26 g (5.5 mmole) of dimethylphenoxycarbonylphosphonate and 2.52 g (16.4 mmole) of bromotrimethylsilane were stirred at room temperature overnight in a dried flask. Volatile components were evaporated *in vacuo* (1 mm) and the residue was stirred with 20 g (36 meq) of Amberlite IRC 50 (Na^+) in 15 ml of water for 2 hours. The solution was filtered and the ion exchanger was washed (on a column) with 25 ml of water. The combined water solutions were washed with 3 $\times$ 10 ml ether, filtered and evaporated *in vacuo*. The residue was washed with ethanol to give 1.24 g (88%) of the disodium phenoxycarbonylphosphonate. T.l.c. (polyethyleneimine, 1.4M LiCl, molybdate spray): R_f 0.43, single spot. By t.l.c. the compound was estimated to contain < 0.5% of trisodium oxycarbonylphosphonate. Analysis for $C_7H_5Na_2O_5P \times 2/3 H_2O$. Found (calculated): H_2O 4.5 (4.6), Na 17.9 (17.8). Molecular weight by titration 269 (258). NMR (D_2O) δ : 7.08—7.54 (m, C_6H_5).

Example 14

Similar to the description in example 13, the following compounds were prepared and analysed.

a) Disodium *p*-tolylloxycarbonylphosphonate

From dimethyl *p*-tolylloxycarbonylphosphonate. Yield 87%. T.l.c. (1M LiCl) R_f 0.65, single spot. By t.l.c. it can be estimated to contain < 0.5% of trisodium oxycarbonylphosphonate. Analysis for $C_8H_7Na_2O_5P \times 1/3 H_2O$. (After drying *in vacuo*). Found (calculated): H_2O 2.40 (2.26), C 35.95 (36.10), H 3.09 (2.65), P 11.44 (11.64). NMR (D_2O) δ : 2.35 (CH_3), 7.0—7.4 (C_6H_4). IR (KBr) cm^{-1} : 1720 (CO), 1210, 1170, 1150 and 980.

b) Disodium *p*-methoxyphenoxycarbonylphosphonate

From diethyl *p*-methoxyphenoxycarbonylphosphonate. Yield 85%. T.l.c. (1M LiCl) R_f 0.45, single spot. By t.l.c. the compound was estimated to contain < 0.5% of trisodium oxycarbonylphosphonate. Analysis for $C_8H_7O_5Na_2P \times H_2O$. Found (calculated) C 32.92 (32.67), H 2.67 (3.08), P 10.44 (10.53).

NMR (D_2O) δ : 3.80 (s, CH_3O), 6.9—7.3 (C_6H_4).

c) *Disodium p-chlorophenoxyphosphonate*

From 5.8 g (20 mmole) of diethyl 4-chlorophenoxyphosphonate and 12.5 g (80 mmole) of bromotrimethylsilane, 5.0 g (89%) of disodium 4-chlorophenoxyphosphonate was obtained. T.l.c. R_f = 0.40. Apparently the compound decomposes during thin layer chromatography (1M LiCl, 3 hours) and a tailing of the single spot can be detected. By t.l.c. the compound can be estimated to contain 1—2% of trisodium oxycarbonylphosphonate. Another synthesis gave a yield of 4.4 g (78%), after drying in a desiccator. T.l.c. R_f 0.37. By t.l.c. the compound was estimated to contain <1% of trisodium oxycarbonylphosphonate. Tailing of the compound obscured any lower detection limit. Analysis for $C_7H_4ClNa_2O_5P$. Found (calculated): C 29.15 (29.97), H 1.73 (1.44), P 11.13 (11.04). NMR (D_2O) δ : 7.1—7.6 (C_6H_4).

d) *Disodium 3,4-dichlorophenoxyphosphonate*

From 5.0 g (17 mmole) of dimethyl 3,4-dichlorophenoxyphosphonate. By t.l.c. the crude product (4.8 g) was estimated to contain <1% of trisodium oxycarbonylphosphonate and approximately 5% of inorganic phosphate (PO_4^{3-}). This crude product was used for the first biological tests. The crude product (2.8 g) was purified by dissolving in 6.5 ml of distilled H_2O and 13 ml of ethanol was slowly added. The precipitate was filtered off, and about 150 ml of ethanol was added to the solution to give a new precipitate. This precipitate was collected and passed through one more precipitation cycle to give purified disodium 3,4-dichlorophenoxyphosphonate. T.l.c. R_f = 0.33, single spot. Apparently the product slowly decomposes during thin layer chromatography (1 m LiCl, 3 hours) and a very weak tailing of the single spot can be detected. By t.l.c. the compound can be estimated to contain <1% of trisodium oxycarbonylphosphonate. Analysis for $C_7H_3Cl_2Na_2O_5P \times 1/2 H_2O$ (After drying *in vacuo*). Found (calculated): H_2O 2.69 (2.78) C 25.83 (25.95), H 1.18 (0.93), P 9.40 (9.56). NMR (D_2O) δ : 7.3—7.7 (C_6H_3). IR (KBr) cm^{-1} : 1710 (CO) 1150 and 990 (PO_4^{3-}).

e) *Disodium p-(ethoxycarbonyl)phenoxyphosphonate*

From 6.6 g (20 mmole) of diethyl p-(ethoxycarbonyl)phenoxyphosphonate. The crude product (5.4 g) was purified by precipitation from water: 5.1 g was dissolved in 10 ml of water and filtered. 20 ml of ethanol was added and the precipitate was filtered. Another 200 ml of ethanol was added to the filtrate and the new precipitate was collected, washed with ethanol and ether and dried *in vacuo*. Yield 1.4 g (22%). T.l.c. (1M LiCl) R_f 0.47. By t.l.c. the compound was estimated to contain <0.4% of trisodium oxycarbonylphosphonate. NMR (D_2O) δ : 1.37 (t, J 7Hz, CH_3), 4.35 (1, J 7Hz, CH_2), 7.35 and 8.02 (doublets, J 9Hz).

Triesters of hydroxycarbonylphosphonic acid used as starting materials for the synthesis of the various di- and mono esters of the same acid, may be prepared by known methods as described in A—J and S above. Below follows, in addition to the examples 1 and 2 already given, further examples of such syntheses.

Example 15

Analogous to the descriptions in examples 1 and 2 the following compounds were prepared by heating the phosphite triester and the chloroformate ester at a temperature from 20 to 130° for 1 to 15 hours.

a) *Ethyl p-methoxyphenyl phenoxyphosphonate*

From 24.4 g (0.10 mole) of diethyl p-methoxyphenylphosphite and 31.2 g (0.20 mole) of phenyl chloroformate (130°, 2 hours). n_D^{25} 1.5378 NMR ($CDCl_3$) δ : 1.42 (t, J 7Hz, CH_3-C), 3.80 (s, CH_3O) 4.50 (quintet, J 7Hz, CH_2), 6.76—7.70 (9H). IR (neat) cm^{-1} : 1740, 1590, 1500, 1180, 980 and 920.

b) *Ethyl, p-chlorophenyl phenoxyphosphonate*

From 24.9 g (0.10 mole) of diethyl p-chlorophenylphosphite and 31.3 g (0.20 mole) of phenyl chloroformate (110°, about 15 hours) NMR ($CDCl_3$) δ : 1.47 (t, J 7Hz, CH_3-C), 4.50 (quintet, J 7Hz, CH_2), 7.0—7.7 (aromatic).

c) *Ethyl 2,6-dimethylphenyl methoxycarbonylphosphonate*

From 20.0 g (83 mmole) of diethyl 2,6-dimethylphenylphosphite and 10.0 ml (127 mmole) of methyl chloroformate (100°, 4 hours, Yield 22.2 g (99%). By g.l.c. (3% OV 17 column, 120—280°) only one peak was seen. NMR ($CDCl_3$) δ : 1.35 (t, J 7Hz, CH_3-C), 2.37 (s, CH_3-Ar), 3.92 (s, CO_2CH_3), 4.40 (quintet, J 7Hz, CH_2), 7.03 (s, C_6H_3). An analytical sample was distilled *in vacuo* B.p._{0.04} 125—8°. n_D^{25} 1.4914.

d) *Ethyl, 5-indanyl methoxycarbonylphosphonate*

From 20.0 g (78 mmole) of diethyl 5-indanylphosphite and 10.0 ml (127 mmole) of methyl chloroformate (100°, 4 hours). yield 22 g (99%). By g.l.c. (3% OV17 column, 120—280°) the purity was

estimated to be about 85%. NMR (CDCl₃) δ: 1.40 (t, J 7Hz, CH₃—C) 1.85—2.35 (multiplet, CH₂), 2.80—3.05 (CH₂—C—CH₂), 3.82 (s, CO₂CH₃), 4.42 (quintet, J 7Hz, CH₂O), 6.9—7.3 (C₆H₃).

e) *Methyl p-acetylphenyl p-nitrophenoxycarbonylphosphonate*

- 5 From 3.78 g (17 mmole) of dimethyl p-acetylphenylphosphite and 3.34 g (17 mmole) of p-nitrophenyl chloroformate (freshly recrystallized from n-hexane) (Room temperature, 4 hours). NMR (CDCl₃) δ: 2.63 (s, CH₃CO), 4.20 (d, J 12Hz, CH₃O), 7.5—7.6 and 8.0—8.5 (C₆H₄ + C₆H₄).

Example 16

10 Diethyl 4-methoxyphenoxycarbonylphosphonate

- 18.6 g (0.12 mole) of triethylphosphite was heated at 125—130° in a flask with a reflux condensor. 18.6 g (0.10 mole) of 4-methoxyphenyl chloroformate (prepared according to M. J. Zabik and R. D. Schuetz J. Org. Chem. 32 (1967) 300) was added dropwise. The reaction flask was heated additionally at about 120° for 1 1/2 hours and left at room temperature overnight. The product was
15 distilled to give 25.8 g (89%) of diethyl 4-methoxyphenoxycarbonylphosphonate. B.p._{0.03} 174—8°, n_D²¹ 1.4940. Analysis for C₁₂H₁₇O₆P. Found (calculated): C 49.79 (50.00), H 6.01 (5.95), P 10.54 (10.75). NMR (CDCl₃) δ: 1.42 (t, CH₃), 3.78 (s, OCH₃), 4.13—4.63 (CH₂), 6.77—7.33 (aromatic). IR (neat) cm⁻¹: 1740 (CO), 1275, 1255, 1190, 1030.

Example 17

- 20 Analogous to the description in example 16, the following compounds were prepared by heating the phosphite triester and the chloroformate ester at 80 to 130° for 1 to 10 hours.

a) *Dimethyl phenoxycarbonylphosphonate*

- 25 From 10.0 ml (85 mmole) of trimethylphosphite and 10.0 g (64 mmole) of phenylchloroformate (100°, 2 hours). Yield 11.0 g (75%). B.p._{0.5} 125—7°, n_D²⁵ 1.4907. NMR (CDCl₃) δ: 3.90 and 4.09 (CH₃), 7.10—7.60 (C₆H₅).

b) *Dimethyl p-tolyloxycarbonylphosphonate*

- 30 From 10.3 g (85 mmole) of trimethylphosphite and 10.3 g (60 mmole) of p-tolyl chloroformate (prepared according to M. J. Zabik and R. D. Scheutz J. Org. Chem. 32 (1967) 300). (100°, 2 hours) yield 93%. B.p._{0.2} 131°, n_D²⁰ 1.4972. Analysis for C₁₀H₁₃O₅P. Found (calculated): C 49.37 (49.18), H 5.53 (5.36), P 11.71 (12.69). NMR (CDCl₃) δ: 2.40 (CH₃), 3.92 and 4.12 (CH₃O), 6.97—7.37 (aromatic protons).

- 35 A second distillation gave a yield of about 80%. New analysis: C 49.13 (49.18), H 5.41 (5.36), P 12.71 (12.69).

c) *Diethyl 4-chlorophenoxycarbonylphosphonate*

- 40 From 20 g (0.12 mole) of triethylphosphite and 19.1 g (0.10 mole) of 4-chlorophenyl chloroformate (prepared according to M. J. Zabik and R. D. Scheutz J. Org. Chem. 32 (1967) 300). (125°, 2 hours) yield 26.3 g (90%). B.p._{0.01} 153—8°, n_D²¹ 1.4980. Analysis for C₁₁H₁₁ClO₅P. Found (calculated): C 44.85 (45.14), H 4.83 (4.82), P 10.54 (10.59). NMR (CDCl₃) δ: 1.45 (t, CH₃), 4.17—4.63 (CH₂), 7.03—7.48 (C₆H₄).

45 d) *Dimethyl 3,4-dichlorophenoxycarbonylphosphonate*

- From 10.3 g (85 mmole) of trimethylphosphite and 13.5 g (60 mmole) of 3,4-dichlorophenyl chloroformate (100°, 2 hours). Yield 11.4 g (64%) B.p._{0.04} 164°C n_D²⁰ 1.5271. Solidifies to colourless crystals m.p. 58—9°C. Analysis for C₉H₇Cl₂O₅P. Found (calculated): C 36.06 (36.14), H 3.31 (3.03), Cl 23.58 (23.71), P 10.50 (10.36). NMR (CDCl₃) δ: 3.93 and 4.07 (CH₃O), 7.0—7.6 (C₆H₃). IR (KBr)cm⁻¹:
50 1740 (CO), 1265, 1200, 1165, 1055, 1020

e) *Diethyl 4-(ethoxycarbonyl)phenoxycarbonylphosphonate*

- From 21.6 g (0.13 mole) of triethylphosphite and 22.8 g (0.10 mole) of 4-ethoxycarbonylphenyl chloroformate (120°, 2 hours). Yield 26.0 g (87%) Bp._{0.01} 190—2°. n_D²⁵ 1.4890. Analysis for C₁₄H₁₉O₇P. Found (calculated): C 50.77 (50.91), H 6.20 (5.80), P 9.53 (9.38).
55

f) *Diphenyl ethoxycarbonylphosphonate*

- [According to A. Takamizawa and Y. Sato, Chem. Pharm. Bull. 12 (1964) 398] Yield 97% B.p._{0.03} 153—5°, n_D²⁵ 1.5314.

- 60 Examples of methods used for the synthesis of haloformate esters.

Example 18

3,4-dichlorophenyl chloroformate

- 40.75 g (0.25 mole) of 3,4-dichlorophenol in 135 ml of dry toluene was cautiously added to 240
65 ml (0.46 moles) of a 20% solution of phosgene in toluene. The reaction flask was equipped with a

stirrer, a dry ice condenser and a dropping funnel, and the reaction temperature was 20—25°, 31.5 g (0.26 moles) of N,N-dimethylaniline was added over a period of 45 minutes and the flask was left without stirring for 2 hours. The precipitate was filtered off and washed with 2 x 25 ml of toluene. The combined toluene solutions were cooled on ice and quickly washed with 50 ml of water, 100 ml of 0.1 N HCl and 100 ml of water. The solution was dried over magnesium sulfate and evaporated on a rotary evaporator. The residue was distilled *in vacuo* over a Vigreux column, to give 46.4 g (82%) of 3,4-dichlorophenylchloroformate, bp₂₀ 134°. The product becomes slightly blue and crystallizes in long needles, mp 51—53°C

Example 19

4-Ethoxycarbonylphenyl chloroformate

From 49.9 g (0.3 mole) of 4-hydroxybenzoic acid ethyl ester, 40 ml (0.3 mole) of N,N-dimethylaniline and 0.4 mole of a 20% solution of phosgene in toluene, 54.4 g (79%) of 4-ethoxycarbonylphenyl chloroformate was obtained. Bp 146—146.5°, n_D²⁵ 1.5140. IR (neat)cm⁻¹: 1720 and 1790 (CO).

Further examples of the synthesis of triesters of phosphorous acid, used as starting materials in the preparations of triesters of hydroxycarbonylphosphonic acid, described above:

Example 20

Diethyl p-methoxyphenylphosphite

The synthesis was carried out by the method described by W. G. Bentrude, E. R. Hansen, W. A. Khan, T. B. Min and P. E. Rogers J. Amer. Chem. Soc. 95 2292 (1973) for the preparation of diethyl phenylphosphite.

A solution of 50.0 g (0.364 mole) of phosphorous trichloride in 500 ml of anhydrous ether was stirred (mechanically) under an atmosphere of argon. The temperature was maintained at -20—-15°C during the addition of 37.1 g triethylamine, followed by the slow addition of p-methoxyphenol. 45.19 g (0.364 mole) in 200 ml of dry ether over a period of 2.5 hours. When the addition was complete another portion of triethylamine 73.8 g (0.728 mole), was added, followed by the slow addition of absolute ethanol, 33.5 g (0.728 mole), in 50 ml of dry ether (1.5 hours). The mixture was stirred at room temperature overnight. The mixture was warmed and allowed to reflux for 1 hour. The triethylamine hydrochloride was filtered off and was washed with dry ether. The solvent was removed under reduced pressure. Distillation of the residual oil yielded 48.6 g of diethyl p-methoxyphenylphosphite, bp 110 (1.2 mm)-102 (0.6 mm). Another 4.20 g was obtained at 0.2 mm bp 92—96°C. n_D²⁰ 1.4993. Analysis for C₁₁H₁₇O₄P. Found (calculated): C 54.14 (54.10), H 7.07 (7.02), P 12.74 (12.68). NMR (CDCl₃) δ: 1.26 (t, J 7Hz, CH₃), 3.70 (s, CH₃O), 4.00 (quintet, J 7Hz, CH₂), 6.7—7.1 (m, C₆H₄). IR (neat)cm⁻¹: 2980, 1510, 1220, 1030, 920.

Example 21

Analogously as described in example 20, the following phosphites were prepared.

a) Diethyl p-chlorophenylphosphite

Yield 43%. Bp_{1.5} 102—104°C, n_D²⁵ 1.5047. NMR (CDCl₃) δ: 1.17 (t, J 7Hz, CH₃), 4.00 (quintet, J 7Hz, CH₂), 6.9—7.3 (C₆H₄). IR (neat)cm⁻¹: 2980, 1590, 1490, 1390, 1030, 920.

b) Diethyl 2,6-dimethylphenylphosphite

Yield 29%. Bp_{0.01} 84—5°, n_D²⁵ 1.4951. NMR (CDCl₃) δ: 1.30 (t, J 7Hz, CH₃—C), 2.33 (s, CH₃—Ar), 4.03 (quintet, J 7Hz, CH₂O), 7.00 (s, C₆H₃).

c) Diethyl 5-indanylphosphite

Yield 29%. Bp_{0.01} 140°, n_D²⁵ 1.5102, NMR (CDCl₃) δ: 1.30 (t, J 7Hz, CH₃), 1.95—2.30 (CH₂), 2.97—3.03 (CH₂—C—CH₂), 4.03 (quintet, J 7Hz, CH₂O), 6.7—7.3 (C₆H₃).

d) Dimethyl p-acetylphenylphosphite

Yield 20%. Bp_{0.03} 128—130°, n_D²⁵ 1.5308. Analysis for C₁₀H₁₃O₄P. Found (calculated): C 52.36 (52.64), H 5.74 (5.74), P 13.33 (13.37). NMR (CDCl₃) δ: 2.58 (s, CH₃CO), 3.68 (d, J 11Hz, CH₃O), 7.14 and 7.97 (d, J 9Hz).

Pharmaceutical compositions

The following examples illustrate the preparation of pharmaceutical compositions of the invention. The active substance in case it can form salts, is preferably used in the form of its sodium salt.

0 003 275

Example 22
Aerosol for inhalation

5	Active substance	1.00 g
	Miglyol®	0.20 g
	Frigen® 11/12/113/114	ad 100.0 g

Example 23 Tablets

Each tablet contains:

15	Active substance	20.0 mg
	Maize starch	25.0 mg
	Lactose	190.0 mg
20	Gelatin	1.5 mg
	Talc	12.0 mg
	Magnesium stearate	1.5 mg
25		250.0 mg

Example 24 Suppositories

Each suppository contains:

	Active substance	20.0 mg
35	Ascorbyl palmitate	1.0 mg
	Suppository base (Imhausen H or Witespol®H)	ad 2000.0 mg

Example 25 Syrup

	Active substance (as its sodium salt)	0.200 g
45	Liquid glucose	30.0 g
	Sucrose	50.0 g
	Ascorbic acid	0.1 g
50	Sodium pyrosulfite	0.01 g
	Disodium edetate	0.01 g
	Orange essence	0.025 g
55	Certified colour	0.015 g
	Purified water	ad 100.0 g

0 003 275

Example 26
Injection solution

5	Active substance (as its sodium salt)	0.500 mg
	Sodium pyrosulfite	0.500 mg
	Disodium edetate	0.100 mg
10	Sodium chloride	8.500 mg
	Sterile water for injection	ad 1.00 ml

Example 27
Inhalation solution

15	Active substance	5.00 g
	Sodium pyrosulfite	0.10 g
20	Disodium edetate	0.10 g
	Sodium chloride	0.85 g
25	Purified water	ad 100.0 ml

Example 28
Sublingual tablets

30	Active substance	5.0 mg
	Lactose	85.0 mg
	Talc	5.0 mg
35	Agar	5.0 mg
		100.0 mg

Example 29
Drops

40	Active substance	2.00 g
45	Ascorbic acid	1.00 g
	Sodium pyrosulfite	0.10 g
	Disodium edetate	0.10 g
50	Liquid glucose	50.00 g
	Absolute alcohol	10.00 g
55	Purified water	ad 100.0 ml

35

0 003 275

**Example 30
Syrup**

5	Active substance (as its sodium salt)	0.200 g
	Liquid glucose	30.0 g
	Sucrose	50.0 g
10	Ascorbic acid	0.1 g
	Disodium edetate	0.01 g
	Orange essence with solubilizer	0.25 g
15	Hydrochloric acid to pH 6.0—8.0	
	Purified water	ad 100.0 g

20

**Example 31
Solution for injection**

	Active substance	0.500 mg
25	Disodium edetate	0.100 mg
	Sodium chloride for isotonia q.s.	
	Hydrochloric acid to pH 6.5—8.0	
30	Sterile water for injection	ad 1.00 ml

35

**Example 32
Solution for inhalation**

	Active substance (as its sodium salt)	5.00 g
	Disodium edetate	0.10 g
40	Sodium chloride	0.85 g
	Hydrochloric acid to pH 6.0—8.0	
45	Purified water	ad 100.0 ml

**Example 33
Drops**

50	Active substance (as its sodium salt)	2.00 g
	Citric acid	1.00 g
	Disodium edetate	0.10 g
55	Liquid glucose	50.00 g
	Ethanol 95%	10.00 g
60	Sodium hydroxide and hydrochloric acid to pH 6.2—6.8	
	Purified water	ad 100.0 ml

65

0 003 275

Example 34
Solution for topical use

5	Active substance (as its sodium salt)	2.00 g
	Isopropanol	38.0 g
	Glycerol	13.6 g
10	Hydrochloric acid to pH 5.0—8.5	
	Purified water	ad 100.0 g

Preparations containing 0.2, 0.5 and 1.0 g of active substance.

15
Example 35
Jelly

20	Active substance (as its sodium salt)	4.0 g
	Methocel®	4.0 g
	Methyl paraoxybenzoate	0.12 g
25	Propyl paraoxybenzoate	0.05 g
	Sodium hydroxide and hydrochloric acid to pH 6.8—8.5	
30	Distilled water	ad 100.0 ml

Example 36
Ointment I

35	Active substance (as its sodium salt)	2.5 g
	Cetyltrimethylammonium bromide	0.6 g
	Stearyl alcohol	2.25 g
40	Cetanol	6.75 g
	Liquid paraffine	17.0 g
45	Glycerol	12.0 g
	Hydrochloric acid to pH 6.0—8.5	
	Distilled water	ad 100.0 g

50 Preparations containing 0.2, 0.5, 1.0, and 2.0 g of active substance have also been prepared.

Example 37
Ointment II

55	Active substance (as its sodium salt)	2.5 g
	Polyethylene glycol 1500	50.0 g
	Polyethylene glycol 4000	15.0 g
60	Propylene glycol	ad 100.0 g

65

0 003 275

Example 43
Cream

5	Active substance	3.0 g
	Arlaton®	4.0 g
	Cetanol	2.0 g
10	Stearic acid	2.0 g
	Paraffin oil	2.0 g
	Propylene glycol	2.0 g
15	Glycerol	1.5 g
	Methyl-p-hydroxybensoate	0.06 g
20	Propyl-p-hydroxybensoate	0.03 g
	Sodium Hydroxide	0.002 g
	Hydrochloric acid 2 M to pH 8.0 (water phase)	
25	Distilled water	ad 100 g

Example 44
Jelly

30	Active substance	3.0 g
	Methocel®	2.45 g
35	Glycerol	10.0 g
	Tween®	0.10 g
	Methyl-p-hydroxybensoate	0.06 g
40	Propyl-p-hydroxybensoate	0.03 g
	Sodiumhydroxid	0.002 g
45	Hydrochloric acid 2 M to pH 8.0	
	Distilled water	ad 100 g

50 *Biological tests*

I. Inhibition of virus multiplication in cell culture

A. *Inhibition of herpes simplex type 1 plaque*

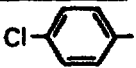
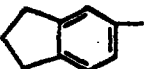
The plaque reduction assay for herpes simplex type 1 was performed on GMK (Green Monkey Kidney) cells as described by Ejereito et al. J. Gen. (Viro 2 (1968) 357. Monolayers on 5 cm petri
55 dishes were used and after virus adsorption the test compound was added in the medium. The results are shown below.

60

65

Inhibition of herpes simplex type 1 plaque on GMK monolayers

5	Test compound	Code	Concentration of test compound (μ M)	Inhibition (%)
10				
15	R_1 R_2 R_3			
		VIS 040	500	>99.9
20		VIS 040	100	>99.9; > 99
	Na	VIS 043	500	>99.9
25		VIS 043	100	>99.9; >99
	Na	VIS 058	500	>99.9; >99.9
30		VIS 058	100	88
	Na	VIS 063	500	>99.9; >99.9
35		VIS 063	100	>99.9
		VIS 063	20	69
40	Na Na	VIS 041	500	>99.9
		VIS 041	100	>99.9; 99
45	Na Na	VIS 059	500	>99.9; >99.9
		VIS 059	100	>99.9
50		VIS 059	20	95
		VIS 059	5	57
55	Na Na	VIS 067	500	>99.9; >99.9
		VIS 067	100	99
		VIS 067	20	87
60		VIS 067	5	57

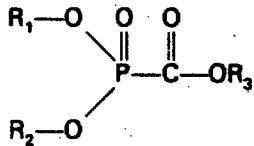
Test compound	Code	Concentration of test compound (μ M)	Inhibition (%)
$ \begin{array}{c} R_1-O \\ \diagup \\ P \\ \diagdown \\ R_2-O \end{array} \begin{array}{c} O \\ \\ P-C \\ \\ O \end{array} \begin{array}{c} O \\ \\ C-OR_3 \end{array} $			
R_1	R_2	R_3	
Na	Cl- 	Na	VIS 066 500 >99.9; >99.9
			VIS 066 100 >99.9
			VIS 066 20 98
			VIS 066 5 89
Na		Na	VIS 442 500 >99.9
Na	Na		VIS 412 500 80; 88
			VIS 412 100 32; 56
Na	Na	CH ₃ - 	VIS 130 500 76; 40; 90
Na	Na	CH ₃ O- 	VIS 239 500 60; 36; 52; 70
Na	Na	Cl- 	VIS 238 500 96; 99
			VIS 238 100 52

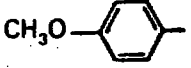
B. Inhibition of influenza (WSN Wilson Smith Neurotropic type A.) plaque

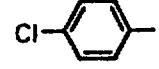
The method for plaque assay of influenza has been described by Bentley et al., Archiv für die Gesamte Virusforschung 33 (1971) 234.

Monolayers of MDCK (Madin Darby Canine Kidney) cells on 5 cm plastic petri dishes were inoculated with 100 plaque-forming units of influenza virus (WSN). After virus adsorption, 5 ml of agarose overlay containing different concentrations of the test compound were added and the plates were incubated at 34°C for 4 days. The plaques formed at this time were counted. The results are shown below.

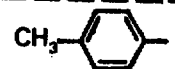
Inhibition of influenza (WSN Wilson Smith Neurotropic type A) plaque on GMK monolayers.

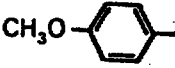
5	Test compound	Code	Concentration of test compound (μ M)	Inhibition (%)
10				
15	R ₁	R ₂	R ₃	
				VIS 040 500 >99
				VIS 040 100 90
20	-----			
	Na			VIS 043 500 >99.9; >99
				VIS 043 100 84; 90; >99.9
25				VIS 043 20 62; 47

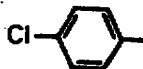
30	Na	CH ₃ O- 		VIS 058 500 >99.9
				VIS 058 100 84

35	Na	Cl- 		VIS 063 500 >99.9
				VIS 063 100 72

40	Na		Na	VIS 041 500 >99.9
				VIS 041 20 60; 28

45	Na	CH ₃ - 	Na	VIS 059 500 >99.9; 91; 92
				VIS 059 100 86; 38
				VIS 059 20 58; 36

50	Na	CH ₃ O- 	Na	VIS 067 500 73; >99.9; >99.9
				VIS 067 100 58

55	Na	Cl- 	Na	VIS 066 500 >99.9; >99.9
				VIS 066 100 54

60	Na		Na	VIS 442 500 94

II. Inhibition of cutaneous herpes on guinea pigs

The effect on cutaneous herpes simplex type 1 infections have been measured in a guinea pig model described by Hubler et al. J. Invest Dermatol 69 (1974) 92. The compounds have been tested as topical applications of 30 μ l of 2% solution of the compound in 45% (v/v) isopropanol, 10% (v/v) glycerol and 45% water (v/v) twice daily for 3 days starting 4 hours after infection. The appearance of an infected treated area and a similar infected untreated (only isopropanolglycerol-water) area was scored daily on a scale from 0 to 3. The total effect is judged from the score at day 5.

10	Test Compound	Code	Score at day 5			
15				treated	untreated	
20	R ₁	R ₂	R ₃			
	Na	Na	phenyl	VIS 412/2	0	3
25	Na			VIS 058	2 and 0 respect. in two experiments	3 ^{x)}
	Na			VIS 063	2 and 3 respect. in two experiments	3 ^{x)}
30	Na			VIS 043 ²⁾	0	3
35				VIS 040 ²⁾	0	3
	Na		Na	VIS 059 ¹⁾	1 and 2, respect. in two experiments	3 ^{x)}
40	Na		Na	VIS 066 ¹⁾	2 and 0, respect in two experiments	3 ^{x)}
45	Na		Na	VIS 067 ¹⁾	1 in each of two experiments	3 ^{x)}
	Na		Na	VIS 041 ²⁾	0	3
50	Na	Na		VIS 412 ²⁾	0	3

1) Tested in 0.1% Tween 80—10% aqueous glycerol

x) In each of two experiments

55 2) Start of treatment 24 hours after infection

III. Stability test

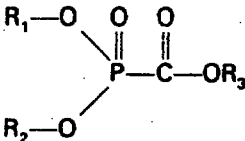
The acid stability was investigated by dissolving 5 mg of each compound in 1 ml of 0.1 N HCl in a test tube. For use as references 0.2 ml of each solution was withdrawn, immediately treated with 0.2 ml of a 10% aqueous solution of NaHCO₃ and frozen. The remaining 0.8 ml of each solution was incubated at 37°C for 2 hours. After incubation, 0.8 ml of a 10% aqueous solution of NaHCO₃ was added to each solution and the solutions were frozen. The incubated compounds and the reference compounds were lyophilized to dryness and redissolved in distilled H₂O, 0.2 ml and 1.0 ml respectively, for each reference solution and incubation solution. The solutions were applied to silica gel (Merck 65 PF₂₅₄, 20 x 20 cm) and polyethylene imine (Macherey-Nagel PEI, 20 x 20 cm) thin layer plates. A total

of 20 μ l of the reference solutions (100 μ g compound) and 25 μ l of the incubated solutions (100 μ g compound) were applied. To each plate was also added, as references, solutions of phosphorous acid (H_2HOP_3) (5 and 20 μ g) and of trisodiumphosphonoformate (5 and 20 μ g). (Decomposition of phosphonoformic acid at low pH produces phosphorous acid).

The silica gel plates were prepared in duplicate and eluted with a solution composed of methanol — 10% aq ammonia — trichloroacetic acid — water (50—15—5—3, v/v) and the polyethylene imine plates were eluted with a 1M aq lithium chloride solution. After elution the plates were dried. One of the duplicated silica gel plates was sprayed with 4% aq $(\text{NH}_4)_2\text{MoO}_4$ and the polyethylene imine plates were sprayed with a solution composed of 60% HClO_4 — 0.1N aq HCl — 4% aq $(\text{NH}_4)_2\text{MoO}_4$ — H_2O (5—10—25—80, v/v). The silica gel plates were briefly dried at 80—90°C and sprayed with 1% SnCl_2 in 10% aq HCl . Phosphorous acid and phosphonic acid groups appeared as blue spots on the silica gel plates (System I) and as white spots on the polyethylene imine plates (System II). The remaining duplicate silica gel plates were exposed to iodine vapour for detection of di- and triesters of phosphonoformic acid.

	R_f System I	R_f System II
Phosphorous acid	0.31	0.71
Na_3 -phosphonoformate	0	0.21

The formation of phosphorous acid and phosphonoformic acid in each incubated solution was estimated and the results are given below. The figures for the non-incubated reference compounds are given in parenthesis.

25						
	Test compound	Code	Estimated formation of phosphorous acid (μg)		Na-phosphono formate (μg)	
30						
35						
	R₁ R₂ R₃					
	Na			VIS 043	N.D.(N.D.)	N.D.(N.D.)
40	Na	Na	Na	EHB 776	20 (N.D.)	(reference)

N.D. = not detectable
(much less than 5 μ g)

IV. In vivo metabolism.

Metabolization of compounds of the invention was tested in NMRI 19—20 g male mice. The test compound (10 μ mol) was dissolved in 0.5 ml saline and injected intraperitoneally. Two mice kept in one cage (for metabolism experiment) were used for each compound. The urine obtained from the two mice on day 1, 2 and 3 after the injections was collected. The urine was diluted with Tris-HCl buffer (pH 7.9) to a constant volume of 1 ml. This volume was then diluted 1:500, 1:5000 and 1:50000 with the same buffer and assayed for phosphonoformic acid activity on cell-free influenza polymerase. The assay mixture which includes Mn^{2+} and assay conditions are described by Bishop, Obijeski and Simpson, J. Virol. 8, 66 (1971). Phosphonoformic acid in diluted urine gave 50% inhibition at 0.5 μ M in this assay and was used as a standard to estimate the amount of phosphonoformic acid activity formed in the urine from compounds of the invention.

Test compound	Recovered phosphonoformic acid activity in urine		
	(μmol phosphonoformic acid)		
	Day 1	Day 2	Day 3
5			
10			
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{NaO}-\text{P}-\text{C}-\text{O}-\text{C}_6\text{H}_4-\text{CH}_3 \\ \\ \text{ONa} \end{array}$ VIS 130	1.25	0.25	0.10
15			
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{NaO}-\text{P}-\text{C}-\text{ONa} \\ \\ \text{O}-\text{C}_6\text{H}_5 \end{array}$ VIS 041	1.00	0.25	0.25
20			
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{NaO}-\text{P}-\text{C}-\text{ONa} \text{ (reference)} \\ \\ \text{ONa} \end{array}$	1.25	0.13	<0.01
25			

Acute toxicity

A preliminary acute toxicity test was carried out in mice. Groups of two male mice of the NMRI strain weighing 20—21 g received the test compound in doses of 62.5—500 mg/kg ip. The compound was given as a solution in 0.9% NaCl. The number of animals dead 24 hours after injection was as follows.

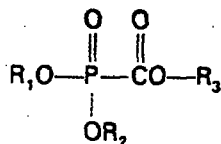
Test compound	Dose mg/kg ip	No of animals dead	
		No of animals injected	
35			
40			
$\begin{array}{c} \text{NaO} \quad \text{O} \quad \text{O} \\ \diagdown \quad \parallel \quad \parallel \\ \text{P}-\text{C}-\text{O}-\text{C}_6\text{H}_5 \\ \diagup \\ \text{NaO} \end{array}$	62.5	0/2	
	125	0/2	
	250	0/2	
45	500	0/2	
46			
$\begin{array}{c} \text{Na} \quad \text{O} \quad \text{O} \\ \diagdown \quad \parallel \quad \parallel \\ \text{P}-\text{C}-\text{O}-\text{C}_6\text{H}_5 \\ \diagup \\ \text{O}-\text{C}_6\text{H}_5 \end{array}$	62.5	0/2	
50	125	0/2	
	250	0/2	
55	500	0/2	
56			
$\begin{array}{c} \text{Na} \quad \text{O} \quad \text{O} \\ \diagdown \quad \parallel \quad \parallel \\ \text{P}-\text{C}-\text{ONa} \\ \diagup \\ \text{O}-\text{C}_6\text{H}_5 \end{array}$	62.5	0/2	
60	125	0/2	
	250	0/2	
65	500	0/2	
66			
$\begin{array}{c} \text{Na} \quad \text{O} \quad \text{O} \\ \diagdown \quad \parallel \quad \parallel \\ \text{P}-\text{C}-\text{ONa} \\ \diagup \\ \text{O}-\text{C}_6\text{H}_5 \end{array}$ VIS 041	500	0/2	

Discussion of test results

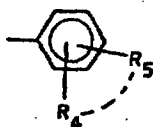
As seen in test I compounds of the invention are active on herpes virus and influenza virus multiplication in cells. As seen in test II compounds of the invention are also active on cutaneous herpes in the guinea pig. According to the stability test III, compounds of the invention are more stable than trisodium phosphonoformate in 0.1 M aqueous HCl, which is a model for stability in gastric juice, and the compounds of the invention should therefore be more suitable for oral administrations than phosphonoformic acid and physiologically acceptable salts thereof. The test on in vivo metabolism IV shows that compounds of the invention are metabolized to phosphonoformic acid measured as phosphonoformic acid activity on influenza polymerase. It is also shown in test IV that compounds according to the invention can give such an active metabolite in the urine of mice over a longer time period than trisodium phosphonoformate. Thus compounds of the invention have a prolonged activity in comparison with phosphonoformic acid and its physiologically acceptable salts. The acute toxicity test shows that compounds of the invention have a low acute toxicity, i.e. high LD50 values. In conclusion compounds of the invention have antiviral effects on herpes and influenza viruses and low toxicity. Furthermore compounds of the invention can be bio-transformed to phosphonoformic acid or ionized forms thereof which have strong activities against viral functions and virus multiplication.

Claims

1. A compound of the formula



wherein each of R_1 , R_2 and R_3 , which are the same or different, is hydrogen or a phenyl group of the formula



wherein each of R_4 and R_5 , which are the same or different, is hydrogen, halogen, alkyl having 1, 2, or 3 carbon atoms, alkoxy having 1, 2, or 3 carbon atoms, alkoxycarbonyl having 2—7 carbon atoms; or alkylcarbonyl having 2—7 carbon atoms; or R_4 and R_5 together form a straight saturated alkylene chain having 3 or 4 carbon atoms and being bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring; provided that one of R_1 and R_2 is a phenyl group of the formula II when R_3 is H; and physiologically acceptable salts and optical isomers thereof.

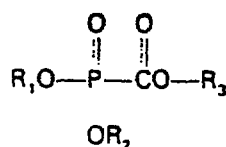
2. A compound according to claim 1 wherein R_1 and/or R_2 is H.
3. A compound according to claim 1 wherein R_3 is H.
4. A compound according to any of claims 1—3 wherein the radical II is a monosubstituted phenyl group.
5. A compound according to any of claims 1—3 wherein the radical II is a disubstituted phenyl group.
6. A compound according to any of claims 1—3 wherein R_4 and R_5 in the radical II together are trimethylene or tetramethylene.
7. A compound according to any of claims 1—3 wherein the radical II is an unsubstituted phenyl group.
8. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-methylphenyl.
9. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-methoxyphenyl.
10. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-chlorophenyl.
11. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 3,4-dichlorophenyl.
12. A compound according to claim 1 wherein the radical R_1 is H, R_2 is phenyl and R_3 is phenyl.
13. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-methoxyphenyl and R_3 is phenyl.
14. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-chlorophenyl and R_3 is phenyl.
15. A compound according to claim 1 wherein the radical R_1 is phenyl, R_2 is phenyl and R_3 is phenyl.

Discussion of test results

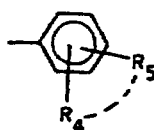
As seen in test I compounds of the invention are active on herpes virus and influenza virus multiplication in cells. As seen in test II compounds of the invention are also active on cutaneous herpes in the guinea pig. According to the stability test III, compounds of the invention are more stable than trisodium phosphonoformate in 0.1 M aqueous HCl, which is a model for stability in gastric juice, and the compounds of the invention should therefore be more suitable for oral administrations than phosphonoformic acid and physiologically acceptable salts thereof. The test on in vivo metabolism IV shows that compounds of the invention are metabolized to phosphonoformic acid measured as phosphonoformic acid activity on influenza polymerase. It is also shown in test IV that compounds according to the invention can give such an active metabolite in the urine of mice over a longer time period than trisodium phosphonoformate. Thus compounds of the invention have a prolonged activity in comparison with phosphonoformic acid and its physiologically acceptable salts. The acute toxicity test shows that compounds of the invention have a low acute toxicity, i.e. high LD50 values. In conclusion compounds of the invention have antiviral effects on herpes and influenza viruses and low toxicity. Furthermore compounds of the invention can be bio-transformed to phosphonoformic acid or ionized forms thereof which have strong activities against viral functions and virus multiplication.

Claims

1. A compound of the formula



wherein each of R_1 , R_2 and R_3 , which are the same or different, is hydrogen or a phenyl group of the formula



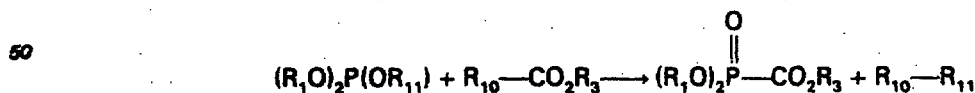
wherein each of R_4 and R_5 , which are the same or different, is hydrogen, halogen, alkyl having 1, 2, or 3 carbon atoms, alkoxy having 1, 2, or 3 carbon atoms, alkoxy carbonyl having 2—7 carbon atoms; or alkyl carbonyl having 2—7 carbon atoms; or R_4 and R_5 together form a straight saturated alkylene chain having 3 or 4 carbon atoms and being bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring; provided that one of R_4 and R_5 is a phenyl group of the formula II when R_3 is H; and physiologically acceptable salts and optical isomers thereof.

2. A compound according to claim 1 wherein R_1 and/or R_2 is H.
3. A compound according to claim 1 wherein R_3 is H.
4. A compound according to any of claims 1—3 wherein the radical II is a monosubstituted phenyl group.
5. A compound according to any of claims 1—3 wherein the radical II is a disubstituted phenyl group.
6. A compound according to any of claims 1—3 wherein R_4 and R_5 in the radical II together are trimethylene or tetramethylene.
7. A compound according to any of claims 1—3 wherein the radical II is an unsubstituted phenyl group.
8. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-methylphenyl.
9. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-methoxyphenyl.
10. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-chlorophenyl.
11. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 3,4-dichlorophenyl.
12. A compound according to claim 1 wherein the radical R_1 is H, R_2 is phenyl and R_3 is phenyl.
13. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-methoxyphenyl and R_3 is phenyl.
14. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-chlorophenyl and R_3 is phenyl.
15. A compound according to claim 1 wherein the radical R_1 is phenyl, R_2 is phenyl and R_3 is phenyl.



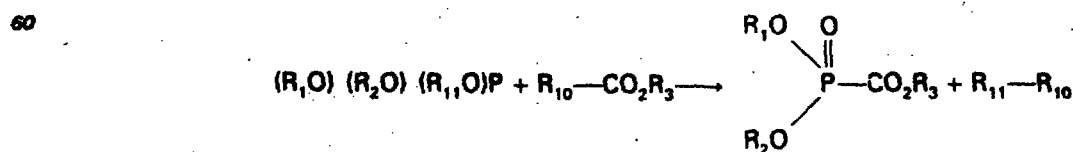
16. A compound according to claim 1 wherein the radical R_1 is 4-methylphenyl, R_2 is 4-methylphenyl and R_3 is phenyl.
17. A compound according to claim 1 wherein the radical R_1 is H, R_2 is phenyl and R_3 is H.
18. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-methylphenyl and R_3 is H.
19. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-methoxyphenyl and R_3 is H.
20. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-chlorophenyl and R_3 is H.
21. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is phenyl.
22. A compound according to claim 1 wherein the radical R_1 is H, R_2 is H and R_3 is 4-ethoxycarbonylphenyl.
23. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-methylphenyl and R_3 is phenyl.
24. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 2,6-dimethylphenyl and R_3 is H.
25. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 5-indanyl and R_3 is H.
26. A compound according to claim 1 wherein the radical R_1 is H, R_2 is 4-acetylphenyl and R_3 is H.
27. A compound according to any of claims 1—14 and 17—26 in the form of a sodium salt.
28. A pharmaceutical preparation comprising as active ingredient a compound according to any of claims 1—27 or a physiologically acceptable salt or an optical isomer thereof.
29. A pharmaceutical preparation according to claim 28 in dosage unit form.
30. A pharmaceutical preparation according to any of claims 28 and 29 comprising the active ingredient in association with a pharmaceutically acceptable carrier.
31. A pharmaceutical preparation according to any of claims 28—30 designed for systemic administration.
32. A compound according to any of claims 1—27 for use in the treatment of diseases caused by viruses in animals including man.
33. A compound according to any of claims 1—27 for use in the treatment of virus-induced neoplastic diseases in animals including man, by inhibiting the transformation of virus-infected cells.
34. A compound according to any of claims 1—27 for use in the treatment of diseases caused by viruses in animals including man, by inhibiting the activity of viral polymerase.
35. A compound according to any of claims 1—27 for use in inhibiting the activity of reverse transcriptases of viruses in animals including man.
36. A compound according to any of claims 1—27 for use in inhibiting the multiplication of virus, in particular herpes-viruses, influenza virus and hepatitis B virus, and retroviruses in animals including man.
37. A compound according to any of claims 1—27 for use in inhibiting the growth of virus-transformed cells in animals including man.
38. A compound according to any of claims 1—27 for use in the treatment of virus-induced neoplastic diseases in animals including man, by inhibiting the multiplication of tumor viruses.
39. A compound according to any of claims 1—27 for use in the treatment of virus-induced neoplastic diseases in animals including man by inhibiting the activity of reverse transcriptase.
40. A compound according to any of claims 1—27 for use in the treatment of neoplastic diseases in animals including man.
41. A process for the preparation of compounds as defined in claim 1 by known methods such as

A. Reacting formic acid ester compounds with phosphite triester according to the formula:



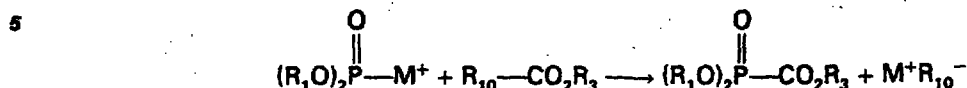
wherein R_1 and R_2 have the meaning given above, R_{10} is a leaving group suitable for Arbuzow type reactions, such as for example Cl, Br, I, sulphonate, carboxylate, alkoxide, and R_{11} may be an alkyl, a cycloalkyl, a cycloalkyl-alkyl, a benzyl, an adamantyl or any phosphite esterifying groups suitable for Arbuzow type reactions;

B. Reacting a formic acid ester with a phosphite triester according to the formula:



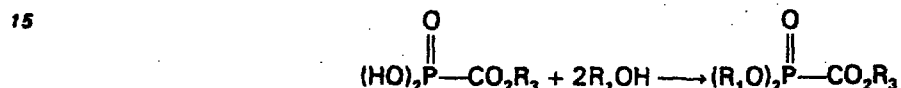
wherein R_1 , R_2 , R_3 , R_{10} and R_{11} have the meaning given above;

C. Reacting a formic acid ester with a phosphite diester salt according to the formula:



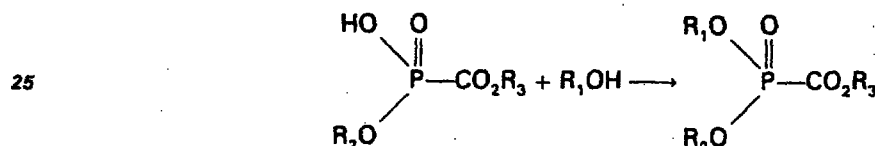
wherein R_1 , R_3 and R_{10} have the meaning given above and M^+ is a cation, preferably a metal such as Li^+ , Na^+ or K^+ ;

D. Esterification of the phosphonic acid groups of hydroxycarbonylphosphonic acid monoester according to the formula:



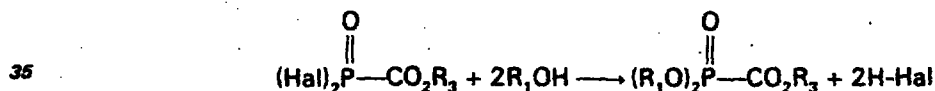
wherein R_1 and R_3 have the meaning given above;

E. Esterification of hydroxycarbonylphosphonic acid diester according to the formula:



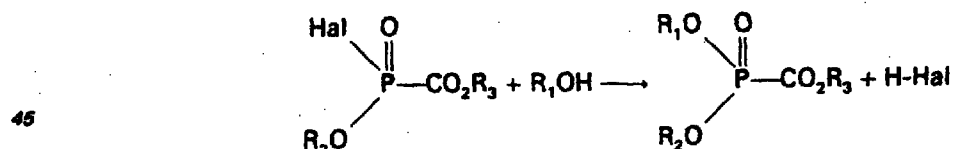
wherein R_1 , R_2 and R_3 have the meaning given above;

F. Reacting a hydroxycarbonylphosphonic acid dihalide ester according to the formula:

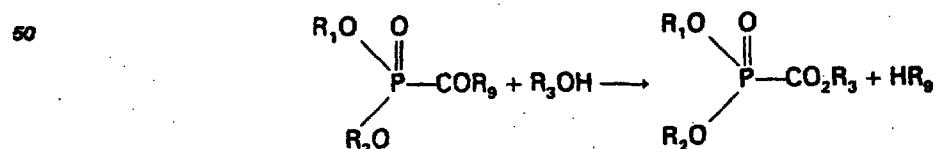


wherein Hal is Cl, Br or I and R_1 and R_2 have the meaning given above;

G. Reacting a hydroxycarbonylphosphonic acid monohalide diester according to the formula:

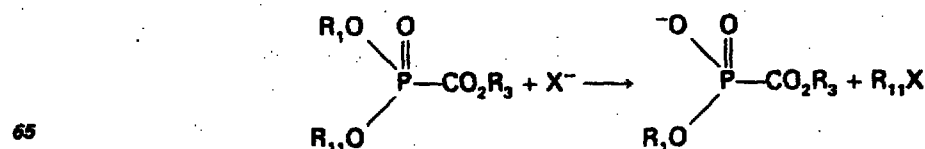


wherein Hal is Cl, Br, or I and R_1 , R_2 and R_3 have the meaning given above;



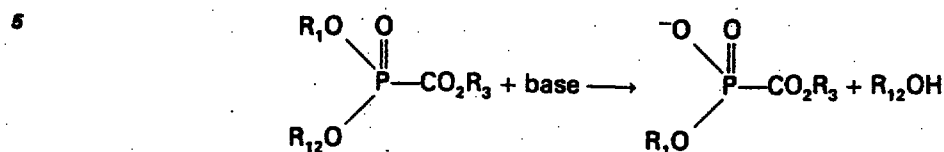
wherein R_1 , R_2 and R_3 have the meaning given above and R_9 is a suitable activating moiety, known *per se* as a good leaving group in substitution reactions on activated carboxylic acid groups;

J. Reacting a hydroxycarbonylphosphonic acid triester with an iodide or a bromide anion, according to the formula:



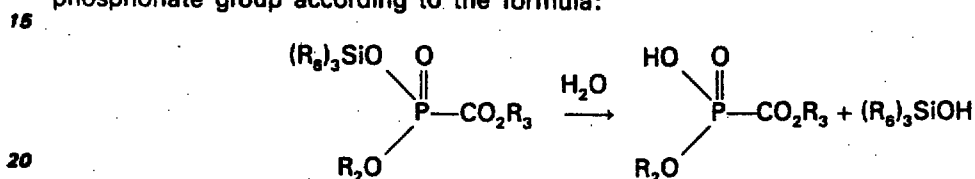
wherein X is Br or I and R_1 , R_3 and R_{11} have the meaning given above;

K. Hydrolysing a hydroxycarbonylphosphonic acid triester with a base according to the formula:



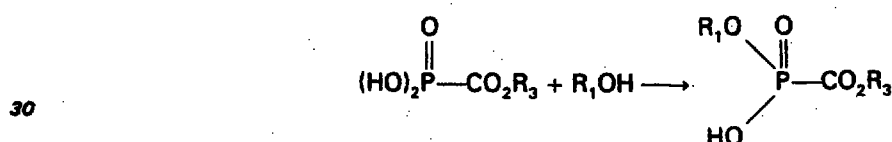
wherein R_1 and R_3 have the meaning given above, and R_{12} is a hydrolyzable phosphate ester group;

L. Aqueous hydrolysis of a hydroxycarbonylphosphonic acid triester, containing one silyl esterified phosphonate group according to the formula:



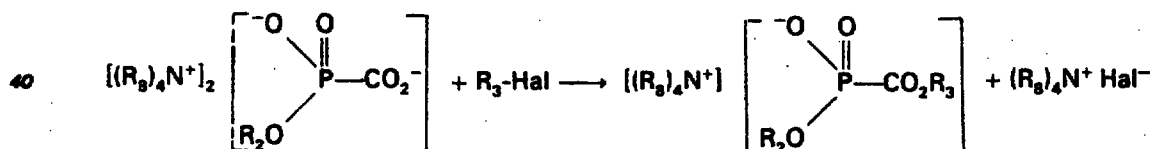
where R_2 and R_3 have the meaning given above and R_6 is an inert organic radical, preferably an organic group such as for example CH_3 ;

M. Reacting hydroxycarbonylphosphonic acid monocarboxylic esters according to the formula:



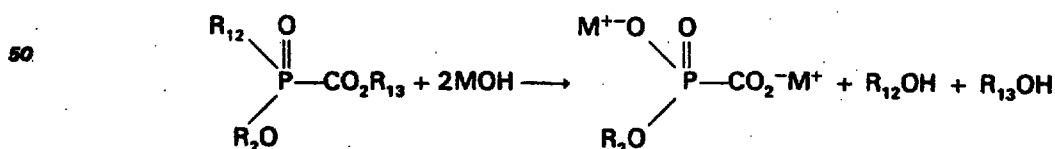
wherein R_1 and R_3 have the meaning given above;

N. Reacting hydroxycarbonylphosphonic acid mono-P ester with an esterifying halide, using a tetra-alkylammonium salt as a catalyst, according to the formula:



wherein Hal is Cl, Br or I, R_2 and R_3 have the meaning given above and R_6 is an alkyl radical such as for example n-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl;

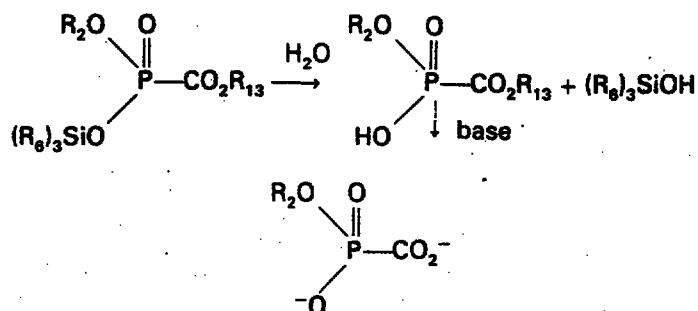
O. Hydrolyzing a hydroxycarbonylphosphonic acid triester according to the formula:



wherein M is a cation such as NH_4^+ or Li^+ , Na^+ or K^+ , R_2 and R_{12} have the meaning given above, R_{13} has the meaning given R_{12} and R_{12} and R_{13} may be the same or different;

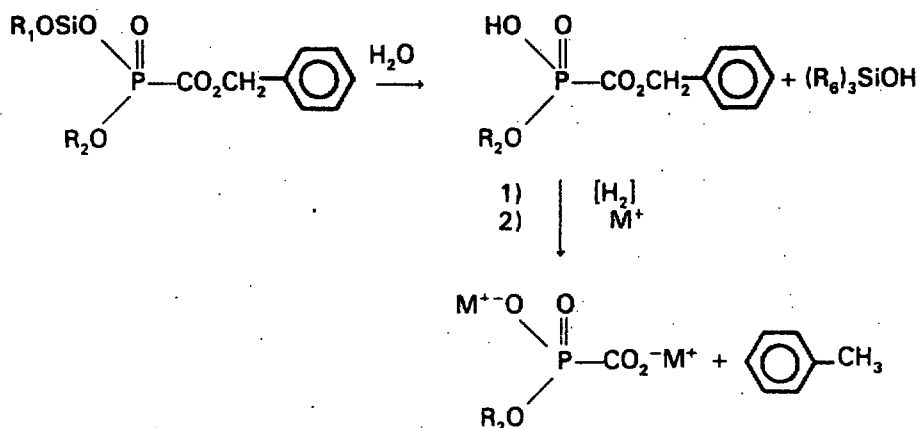
P. By the stepwise deesterification of a phosphonic acid trisubstituted silyl ester group, and the carboxylic acid ester group, of hydroxycarbonylphosphonic acid triester, according to the formula:





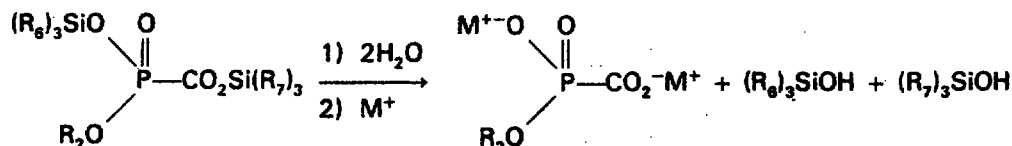
wherein R_2 , R_6 and R_{13} have the meaning given above, and the silyl ester group is preferably a group such as exemplified above in method L;

Q. By the stepwise deesterification of the silyl and benzyl ester group of aryl silyl benzyloxycarbonylphosphonate according to the formula:



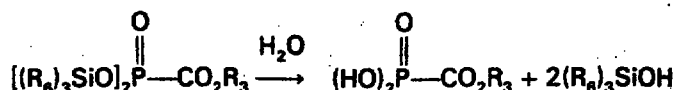
wherein M^+ is NH^+ or a metal such as for example Li^+ , Na^+ or K^+ , and R_2 and R_6 have the meaning given above;

R. By the deesterification of the bis-silylester groups (on the phosphonic and on the carboxylic acid groups) of hydroxycarbonylphosphonic acid triester according to the formula:



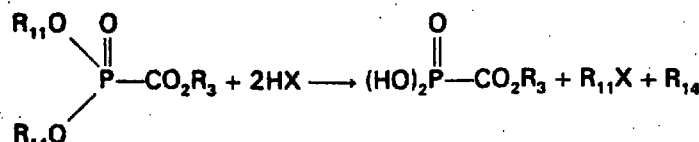
R_2 has the meaning given above, R_6 and R_7 are inert organic radicals, the same or different, preferably they are the same and a group such as for example CH_3 ;

S. Aqueous hydrolysis of a hydroxycarbonylphosphonic acid triester, containing two silyl esterified phosphonate groups, according to the formula:



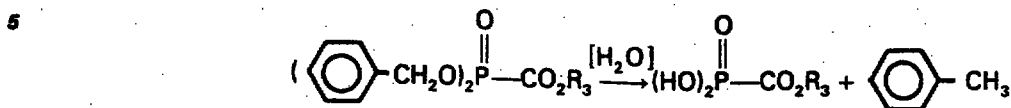
wherein R_3 and R_6 have the meaning given above;

T. Reacting a triester of hydroxycarbonylphosphonic acid with hydrohalide acid according to the formula:



wherein R_3 , R_{11} and R_{14} have the meaning given above and X is Cl, Br or I;

U. Hydrogenating dibenzyl, aryloxycarbonylphosphate according to the formula:



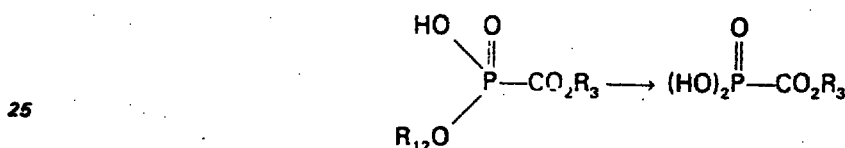
10 wherein R_3 has the meaning given above.

V. Reacting hydroxycarbonylphosphonic acid with an esterifying halide, using a tetraalkylammonium salt as a catalyst, according to the formula



Hal is Cl, Br or I. R_3 has the meaning given above and R_8 is an alkyl radical, such as for example n-butyl, n-pentyl, n-hexyl, n-heptyl and N-octyl;

20 W. Reacting hydroxycarbonylphosphonic acid diesters according to the formula:



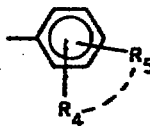
wherein R_3 and R_{12} have the meaning described above; whereafter the compound of the formula I thus obtained if desired is converted to a physiologically acceptable salt and/or resolved into the optical isomers.

Revendications

35 1. Composé de formule



45 dans laquelle chacun des R_1 , R_2 , et R_3 qui sont identiques ou différents, est l'hydrogène ou un groupe phényle de formule



55 dans laquelle chacun des R_4 et R_5 , qui sont identiques ou différents, est l'hydrogène, un halogène, un groupe alkyle ayant 1, 2 ou 3 atomes de carbone, alcoxy ayant 1, 2 ou 3 atomes de carbone, alcoxy-carbonyle ayant de 2 à 7 atomes de carbone, ou alkylcarbonyle ayant de 2 à 7 atomes de carbone; ou R_4 et R_5 forment ensemble une chaîne alkylène saturée, droite, ayant 3 ou 4 atomes de carbone et étant reliée en des positions adjacentes, c'est-à-dire en 2,3- ou 3,4- au noyau phényle, à condition que R_1 ou R_2 soit un groupe phényle de formule II lorsque R_3 est H; et les sels physiologiquement acceptables et les isomères optiques dudit composé.

2. Composé selon la revendication 1, caractérisé en ce que R_1 et/ou R_2 est H.

3. Composé selon la revendication 1, caractérisé en ce que R_3 est H.

60 4. Composé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que le radical II est un groupe phényle monosubstitué.

5. Composé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que le radical II est un groupe phényle disubstitué.

65 6. Composé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que R_4 et R_5 dans le radical II forment ensemble un groupe triméthylène ou tétraméthylène.



7. Composé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que le radical II est un groupe phényle non substitué.
8. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est H et R_3 est le groupe 4-méthylphényle.
- 5 9. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est H et R_3 est le groupe 4-méthoxyphényle.
10. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est H et R_3 est le groupe 4-chlorophényle.
- 10 11. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est H et R_3 est le groupe 3,4-dichlorophényle.
12. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe phényle et R_3 est le groupe phényle.
13. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-méthoxyphényle et R_3 est le groupe phényle.
- 15 14. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-chlorophényle et R_3 est le groupe phényle.
15. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est le groupe phényle, R_2 est le groupe phényle et R_3 est le groupe phényle.
16. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est le groupe 4-méthylphényle, R_2 est le groupe 4-méthylphényle et R_3 est le groupe phényle.
- 20 17. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe phényle et R_3 est H.
18. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-méthylphényle, et R_3 est H.
- 25 19. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-méthylphényle et R_3 est H.
20. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-chlorophényle et R_3 est H.
21. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est H et R_3 est le groupe phényle.
- 30 22. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est H et R_3 est le groupe 4-éthoxycarbonylphényle.
23. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-méthylphényle et R_3 est le groupe phényle.
- 35 24. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 2,6-diméthylphényle et R_3 est H.
25. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 5-indanyle et R_3 est H.
26. Composé selon la revendication 1, caractérisé en ce que le radical R_1 est H, R_2 est le groupe 4-acétylphényle et R_3 est H.
- 40 27. Composé selon l'une quelconque des revendications 1 à 14 et 17 à 26 sous la forme d'un sel de sodium.
28. Composition pharmaceutique, caractérisé en ce qu'elle contient, à titre d'ingrédient actif, un composé selon l'une quelconque des revendications 1 à 27 ou un sel physiologiquement acceptable ou un isomère actif dudit composé.
- 45 29. Composition pharmaceutique selon la revendication 28 sous la forme d'une dose unitaire.
30. Composition pharmaceutique selon l'une quelconque des revendications 28 et 29, caractérisée en ce qu'elle contient l'ingrédient actif associé avec un véhicule pharmaceutiquement acceptable.
- 50 31. Composition pharmaceutique selon l'une quelconque des revendications 28 à 30, conçue pour une administration systémique.
32. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans le traitement des maladies causées par des virus chez les animaux, y compris l'homme.
33. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans le traitement des 55 maladies néoplastiques induites par un virus chez les animaux, y compris l'homme, par inhibition de la transformation des cellules infectées par le virus.
34. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans le traitement des maladies causées par des virus chez les animaux, y compris l'homme, par inhibition de l'activité de la polymérase virale.
- 60 35. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans l'inhibition de l'activité des transcriptases inverses des virus chez les animaux, y compris l'homme.
36. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans l'inhibition de la multiplication des virus, en particulier des virus herpès, du virus de la grippe, du virus de l'hépatite B et des rétrovirus chez les animaux, y compris l'homme.
- 65 37. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans l'inhibition du



développement des cellules transformées par un virus chez les animaux, y compris l'homme.

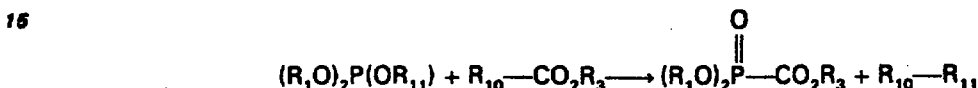
38. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans le traitement des maladies néoplastiques induites par un virus chez les animaux, y compris l'homme, par inhibition de la multiplication des virus tumoraux.

39. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans le traitement des maladies néoplastiques induites par un virus chez les animaux, y compris l'homme, par inhibition de l'activité de la transcriptase inverse.

40. Composé selon l'une quelconque des revendications 1 à 27, utilisable dans le traitement des maladies néoplastiques chez les animaux, y compris l'homme.

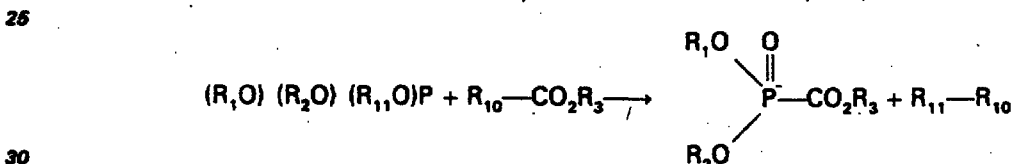
41. Procédé de préparation de composés tels que définis dans la revendication 1, par des procédés connus tels que:

A. Réaction d'un ester de l'acide formique avec un triester de phosphite selon la formule:



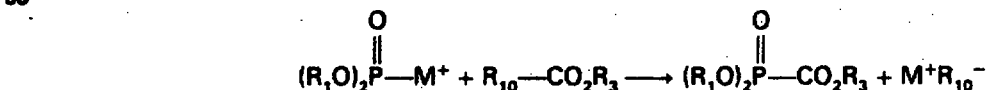
dans laquelle R_1 et R_2 ont les significations indiquées ci-dessus, R_{10} est un groupe éliminable approprié pour des réactions de type Arbuzow, tel que par exemple Cl, Br, I, un groupe sulfonate, carboxylate, alcoxy, et R_{11} peut être un groupe alkyle, cycloalkyle, cycloalkyl-alkyle, benzyle, adamantyle ou tout groupe d'estérification d'un phosphite approprié pour des réactions de type Arbuzow:

B. Réaction d'un ester de l'acide formique avec un triester de phosphite selon la formule:



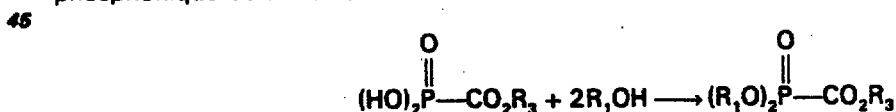
dans laquelle R_1 , R_2 , R_3 , R_{10} et R_{11} ont les significations indiquées ci-dessus;

C. Réaction d'un ester de l'acide formique avec un sel de diester de phosphite selon formule:



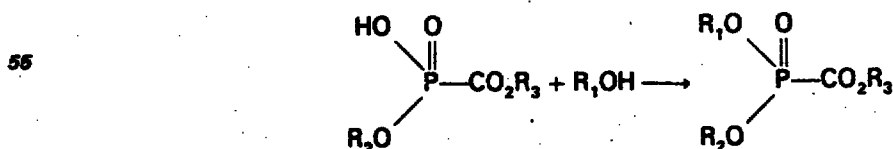
dans laquelle R_1 , R_3 et R_{10} ont les significations indiquées ci-dessus et M^+ est un cation, de préférence un métal, tel que Li^+ , Na^+ ou K^+ ;

D. Estérification des groupes acide phosphonique d'un monoester de l'acide hydroxycarbonylphosphonique selon la formule:



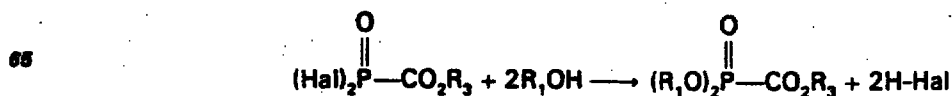
dans laquelle R_1 et R_3 ont les significations indiquées ci-dessus;

E. Estérification d'un diester de l'acide hydroxycarbonylphosphonique selon la formule:



dans laquelle R_1 , R_2 et R_3 ont les significations indiquées ci-dessus.

F. Réaction d'un ester d'un dihalogénure de l'acide hydroxycarbonylphosphonique selon la formule:

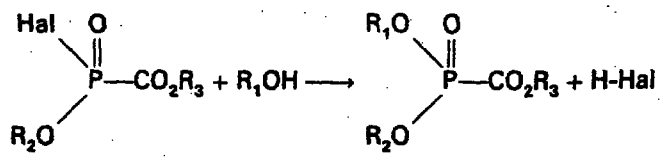


dans laquelle Hal est Cl, Br ou I et R₁ et R₂ ont les significations indiquées ci-dessus;

G. Réaction d'un diester d'un monohalogénure de l'acide hydroxycarbonylphosphonique selon la formule:

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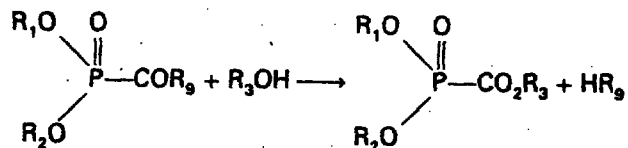


dans laquelle Hal est Cl, Br ou I et R₁, R₂ et R₃ ont les significations indiquées ci-dessus;

H. Réaction d'un diester de l'acide carbonylphosphonique selon la formule:

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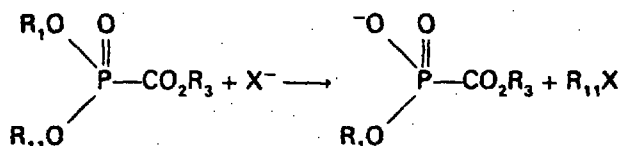


dans laquelle R₁, R₂ et R₃ ont les significations indiquées ci-dessus et R₃ est un radical d'activation approprié connu en soi comme un groupe facilement éliminable dans des réactions de substitution sur les groupes acide carboxylique activés;

25

J. Réaction d'un triester de l'acide hydroxycarbonylphosphonique avec un anion bromure ou iodure, selon la formule:

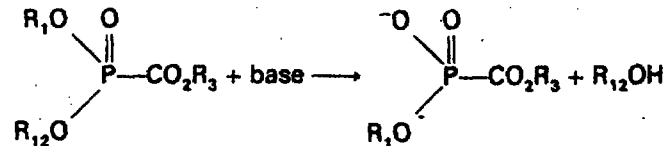
30



dans laquelle X est Br ou I, et R₁, R₃ et R₁₁ ont les significations indiquées ci-dessus;

K. Hydrolyse d'un triester de l'acide hydroxycarbonylphosphonique avec une base selon la formule:

40

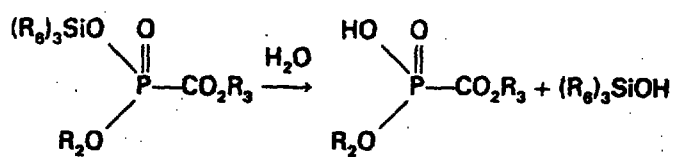


dans laquelle R₁ et R₃ ont les significations indiquées ci-dessus et R₁₂ est un groupe ester phosphate hydrolysable;

L. Hydrolyse aqueuse d'un triester de l'acide hydroxycarbonylphosphonique, contenant un groupe phosphonate estérifié par un radical silyle, selon la formule:

50

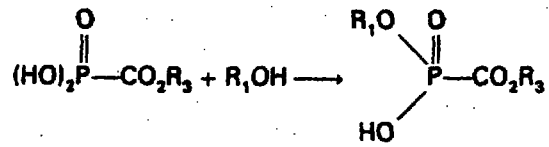
55



dans laquelle R₂ et R₃ ont les significations indiquées ci-dessus et R₆ est un radical organique inerte, de préférence un groupe organique, tel que par exemple CH₃;

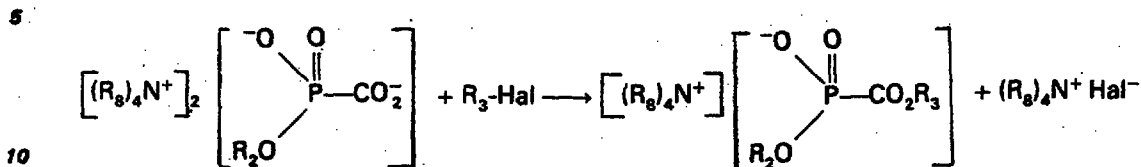
M. Réaction d'un ester monocarboxylique de l'acide hydroxycarbonylphosphonique selon la formule:

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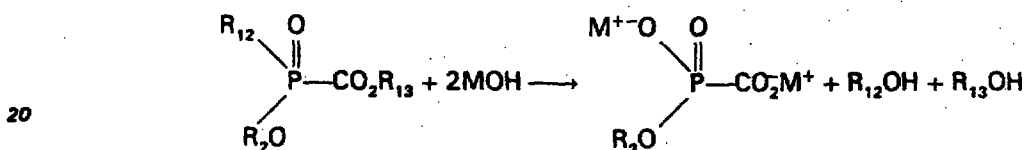
dans laquelle R_1 et R_3 ont les significations indiquées ci-dessus;

N. Réaction d'un mono-P ester de l'acide hydroxycarbonylphosphonique avec un halogénure d'estérification, en utilisant un sel de tétraalkyl-ammonium comme catalyseur, selon la formule:



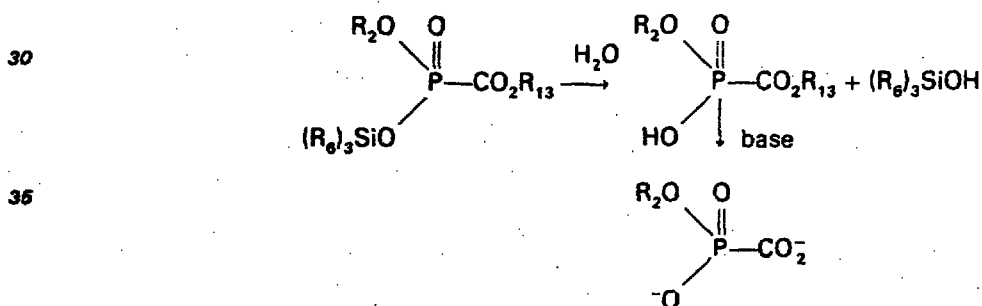
dans laquelle Hal est Cl, Br ou I, R_2 et R_3 ont les significations indiquées ci-dessus et R_8 est un radical alkyle, tel que par exemple n-butyle, n-pentyle, n-hexyle, n-heptyle et n-octyle;

O. Hydrolyse d'un triester de l'acide hydroxycarbonylphosphonique selon la formule:



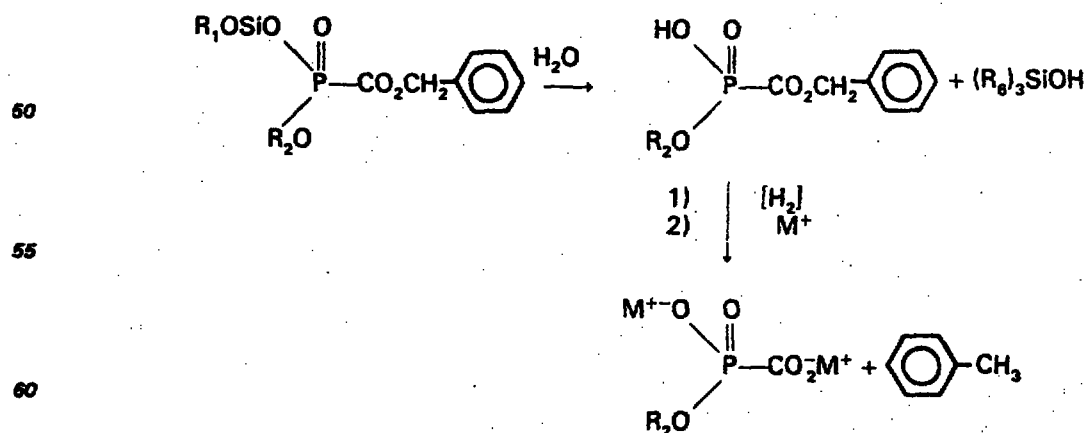
dans laquelle M est un cation, tel que NH_4^+ ou Li^+ , Na^+ ou K^+ , R_2 et R_{12} ont les significations indiquées ci-dessus, R_{13} a la signification indiquée pour R_{12} et R_{12} et R_{13} peuvent être identiques ou différents.

P. Désestérification progressive d'un groupe ester silylique trisubstitué de l'acide phosphonique et du groupe ester acide carboxylique, du triester de l'acide hydroxycarbonylphosphonique, selon la formule:



dans laquelle R_2 , R_6 et R_{13} ont les significations indiquées ci-dessus et le groupe ester silylique est de préférence un groupe tel que celui décrit ci-dessus dans le procédé L;

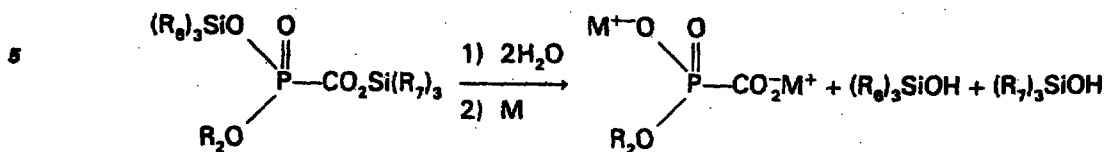
Q. Désestérification progressive du groupe ester silylique et benzylique d'un aryl-silyl-benzyloxy-carbonylphosphonate, selon la formule:



dans laquelle M^+ est NH_4^+ ou un métal, tel que par exemple Li^+ , Na^+ ou K^+ et R_2 et R_6 ont les significations indiquées ci-dessus;

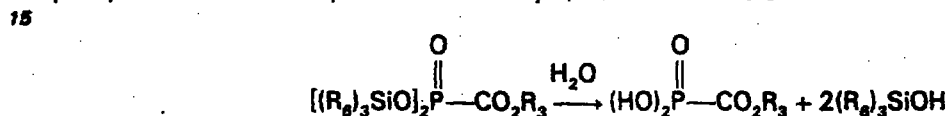


R. Désestérification des groupes ester bis-silylique (sur les groupes acide phosphonique et acide carboxylique) d'un triester de l'acide hydroxycarbonylphosphonique, selon la formule:



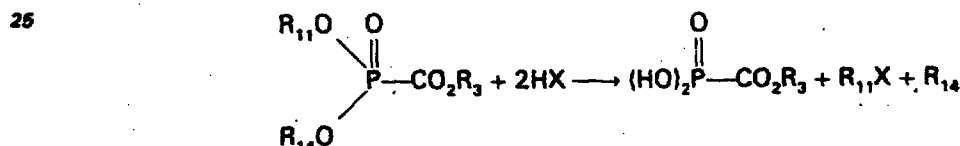
10 dans laquelle R_2 a la signification indiquée ci-dessus, R_6 et R_7 sont des radicaux organiques inertes, identiques ou différents, de préférence identiques et représentent un groupe, tel que par exemple CH_3 ;

S. Hydrolyse aqueuse d'un triester de l'acide hydroxycarbonylphosphonique, contenant deux groupes phosphonate estérifiés par un radical silyle, selon la formule



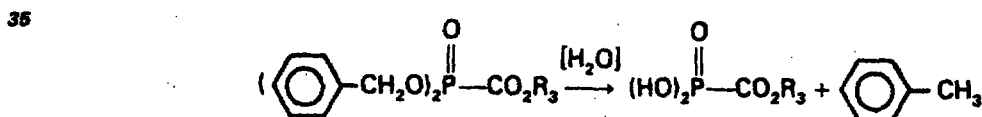
20 dans laquelle R_3 et R_6 ont les significations indiquées ci-dessus;

T. Réaction d'un triester de l'acide hydroxycarbonylphosphonique par un acide hydrohalogéné, selon la formule:



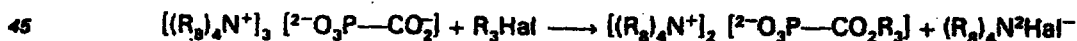
30 dans laquelle R_3 , R_{11} et R_{14} ont les significations indiquées ci-dessus et X est Cl, Br ou I;

U. Hydrogénation d'un dibenzyl-aryloxyphosphonate selon la formule:



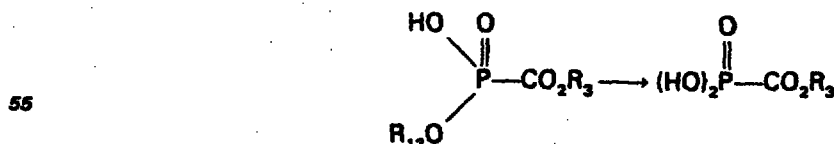
40 dans laquelle R_3 a la signification indiquée ci-dessus;

V. Réaction de l'acide hydroxycarbonylphosphonique avec un halogénure estérifiant, en utilisant un sel de tétraalkylammonium comme catalyseur, selon la formule



dans laquelle Hal est Cl, Br ou I, R_3 a la signification indiquée ci-dessus et R_8 est un radical alkyle, tel que par exemple n-butyle, n-pentyle, n-hexyle, n-heptyle et n-octyle;

50 W. Réaction d'un diester de l'acide hydroxycarbonylphosphonique selon la formule:

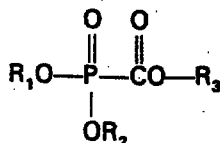


dans laquelle R_3 et R_{12} ont les significations indiquées ci-dessus; après quoi le composé de formule I ainsi obtenu est converti, si nécessaire, en un sel physiologiquement acceptable et/ou résolu en ses isomères optiques.

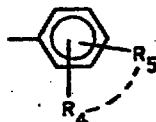


Patentansprüche

1. Verbindung der Formel



worin R_1 , R_2 und R_3 , die gleich oder verschieden sind, jeweils ein Wasserstoff oder eine Phenylgruppe der Formel



bedeuten, worin R_4 und R_5 , die gleich oder verschieden sind, jeweils ein Wasserstoffatom, ein Halogenatom, eine Alkylgruppe mit 1, 2 oder 3 Kohlenstoffatomen, eine Alkoxygruppe mit 1, 2 oder 3 Kohlenstoffatomen, eine Alkoxy-carbonylgruppe mit 2 bis 7 Kohlenstoffatomen oder eine Alkyl-carbonylgruppe mit 2 bis 7 Kohlenstoffatomen bedeuten oder R_4 und R_5 zusammen eine geradkettige gesättigte Alkylkette mit 3 oder 4 Kohlenstoffatomen bilden und in benachbarten Stellungen, d.h. in 2,3- oder 3,4-Stellung an den Phenylring gebunden sind, wobei einer der Reste R_1 und R_2 ein Phenylrest der Formel II ist, wenn R_3 H bedeutet, und deren physiologisch verträgliche Salze und deren optische Isomere.

2. Eine Verbindung nach Anspruch 1, worin R_1 und/oder R_2 H bedeutet.
3. Eine Verbindung nach Anspruch 1, worin R_3 H bedeutet.
4. Eine Verbindung nach einem der Ansprüche 1 bis 3, worin der Rest II ein monosubstituierter Phenylrest ist.
5. Eine Verbindung nach einem der Ansprüche 1 bis 3, worin der Rest II ein disubstituierter Phenylrest ist.
6. Eine Verbindung nach einem der Ansprüche 1 bis 3, worin R_4 und R_5 in dem Rest II zusammen eine Trimethylen- oder Tetramethylengruppe sind.
7. Eine Verbindung nach einem der Ansprüche 1 bis 3, worin der Rest II ein unsubstituierter Phenylrest ist.
8. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 H und der Rest R_3 4-Methylphenyl bedeutet.
9. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 H und der Rest R_3 4-Methoxyphenyl bedeutet.
10. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 H und der Rest R_3 4-Chlorphenyl bedeutet.
11. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 H und der Rest R_3 3,4-Dichlorphenyl bedeutet.
12. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 Phenyl und der Rest R_3 Phenyl bedeutet.
13. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Methoxyphenyl und der Rest R_3 Phenyl bedeutet.
14. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Chlorphenyl und der Rest R_3 Phenyl bedeutet.
15. Eine Verbindung nach Anspruch 1, worin der Rest R_1 Phenyl, der Rest R_2 Phenyl und der Rest R_3 Phenyl bedeutet.
16. Eine Verbindung nach Anspruch 1, worin der Rest R_1 4-Methylphenyl, der Rest R_2 4-Methylphenyl und der Rest R_3 Phenyl bedeutet.
17. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 Phenyl und der Rest R_3 H bedeutet.
18. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Methylphenyl und der Rest R_3 H bedeutet.
19. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Methoxyphenyl und der Rest R_3 H bedeutet.
20. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Chlorphenyl und der Rest R_3 H bedeutet.
21. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 H und der Rest R_3 Phenyl bedeutet.
22. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 H und der Rest R_3 4-



Äthoxycarbonylphenyl bedeutet.

23. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Methylphenyl und der Rest R_3 Phenyl bedeutet.

24. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 2,6-Dimethylphenyl und der Rest R_3 H bedeutet.

25. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 5-Indanyl und der Rest R_3 H bedeutet.

26. Eine Verbindung nach Anspruch 1, worin der Rest R_1 H, der Rest R_2 4-Acetylphenyl und der Rest R_3 H bedeutet.

27. Eine Verbindung nach einem der Ansprüche 1 bis 14 und 17 bis 26 in der Form eines Natriumsalzes.

28. Ein pharmazeutisches Präparat, das als aktiven Bestandteil eine Verbindung nach einem der Ansprüche 1 bis 27 oder ein physiologisch verträgliches Salz oder ein optisches Isomeres derselben enthält.

29. Ein pharmazeutisches Präparat nach Anspruch 28 in der Form von Dosierungseinheiten.

30. Ein pharmazeutisches Präparat nach einem der Ansprüche 28 und 29, das den Aktiven Bestandteil in Verbindung mit einem pharmazeutisch verträglichem Trägermaterial enthält.

31. Ein pharmazeutisches Präparat nach einem der Ansprüche 28 bis 30 für systemische Verabreichung.

32. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Behandlung von durch Viren verursachten Erkrankungen bei Tieren einschließlich Menschen.

33. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Behandlung von virusinduzierten neoplastischen Erkrankungen bei Tieren einschließlich Menschen durch Hemmung der Veränderung von virusinfizierten Zellen.

34. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Behandlung von durch Viren verursachten Erkrankungen bei Tieren einschließlich Menschen durch Hemmung der Aktivität von viraler Polymerase.

35. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Hemmung der Aktivität von Umkehrtranscriptasen von Viren bei Tieren einschließlich Menschen.

36. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Hemmung der Vermehrung von Viren, besonders von Herpes-Viren, Influenza-Viren und Hepatitis-B-Viren sowie Retroviren bei Tieren einschließlich Menschen.

37. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Hemmung des Wachstums von durch Viren veränderten Zellen bei Tieren einschließlich Menschen.

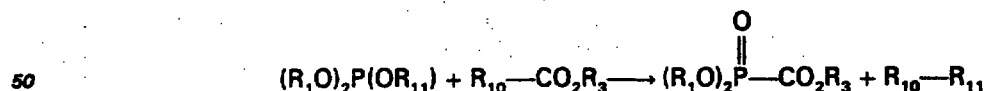
38. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Behandlung von durch Viren induzierten neoplastischen Erkrankungen bei Tieren einschließlich Menschen durch Hemmung der Vermehrung von Tumoviren.

39. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Behandlung von durch Viren induzierten neoplastischen Erkrankungen bei Tieren einschließlich Menschen durch Hemmung der Aktivität von Umkehrtranscriptase.

40. Eine Verbindung nach einem der Ansprüche 1 bis 27 für die Verwendung bei der Behandlung von neoplastischen Erkrankungen bei Tieren einschließlich Menschen.

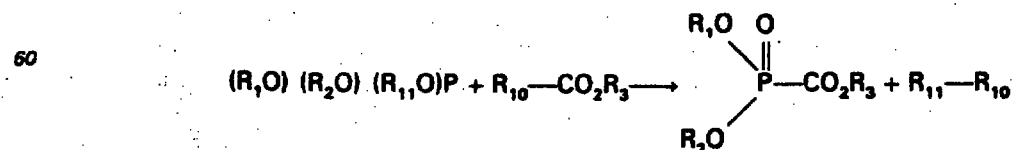
41. Verfahren zur Herstellung von Verbindung nach Anspruch 1 nach an sich bekannten Methoden, wie

A. Umsetzung eines Ameisensäureesters mit einem Phosphittriestern nach der Gleichung



worin R_1 und R_2 die obige Bedeutung haben, R_{10} eine für Arbuzow-Reaktionen geeignete austretende Gruppe, wie beispielsweise Cl, Br, I, Sulphonat, Carboxylat oder Alkoxid, ist und R_{11} eine Alkyl-, Cycloalkyl-, Cycloalkyl-alkyl-, Benzyl-, Adamantyl- oder irgendeine phosphitveresternde Gruppe, die für Arbuzow-Reaktionen geeignet ist, ist, oder

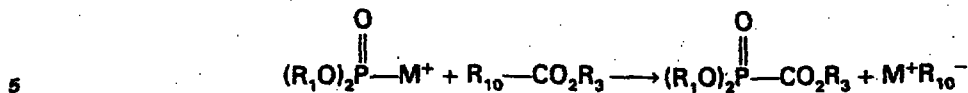
B. Umsetzung eines Ameisensäureesters mit einem Phosphittriestern nach der Gleichung



worin R_1 , R_2 , R_3 , R_{10} und R_{11} die obige Bedeutung haben, oder

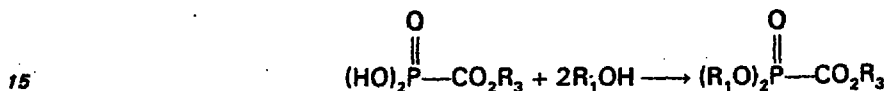


C. Umsetzung eines Ameisensäureesters mit einem Phosphitdiestersalz nach der Gleichung



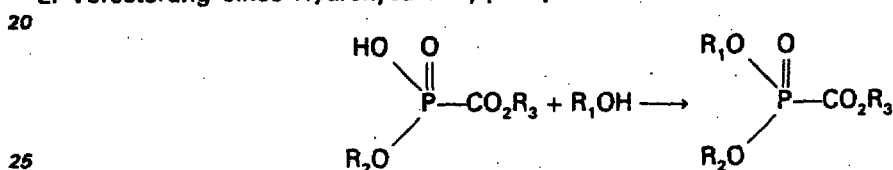
worin R_1 , R_3 und R_{10} die obige Bedeutung haben und M^+ ein Kation, vorzugsweise ein Metall, wie Li^+ , Na^+ oder K^+ ist, oder

10 D. Veresterung der Phosphonsäuregruppen eines Hydroxycarbonylphosphonsäuremonoesters nach der Gleichung



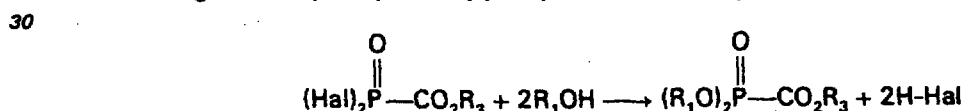
worin R_1 und R_3 die obige Bedeutung haben, oder

E. Veresterung eines Hydroxycarbonylphosphonsäurediesters nach der Gleichung



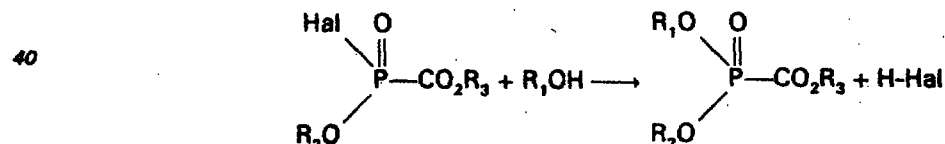
25 worin R_1 , R_2 und R_3 die obige Bedeutung haben, oder

F. Umsetzung eines Hydroxycarbonylphosphonsäuredihalogenidesters nach der Gleichung



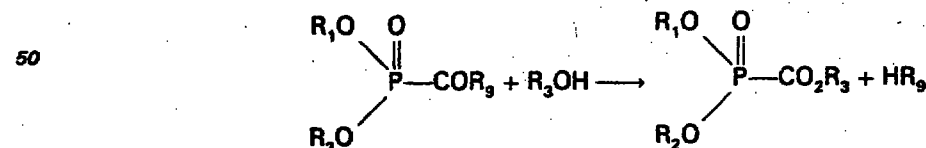
35 worin Hal Cl, Br oder I ist und R_1 und R_2 die obige Bedeutung haben, oder

G. Umsetzung eines Hydroxycarbonylphosphonsäuremonohalogeniddiesters nach der Gleichung



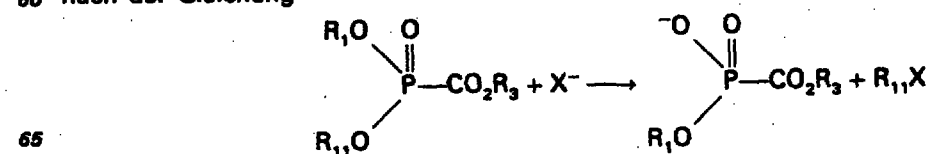
45 worin Hal Cl, Br oder I ist und R_1 , R_2 und R_3 die obige Bedeutung haben, oder

H. Umsetzung eines Carbonylphosphonsäurediesters nach der Gleichung



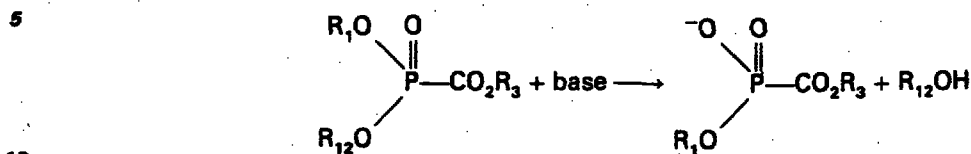
55 worin R_1 , R_2 und R_3 die obige Bedeutung haben und R_3 ein geeigneter aktivierender Rest ist, der an sich als bei Substitutionsreaktionen an aktivierten Carbonsäuregruppen gut austretender Rest bekannt ist, oder

J. Umsetzung eines Hydroxycarbonylphosphonsäuretriesters mit einem Jodid- oder einem Bromidanion nach der Gleichung



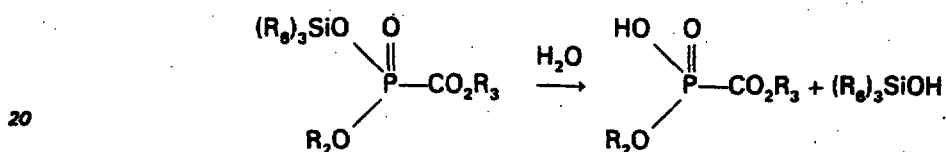
worin X Br oder I ist und R_1 , R_3 und R_{11} die obige Bedeutung haben, oder

K. Hydrolyse eines Hydroxycarbonylphosphonsäuretriesters mit einer Base nach der Gleichung



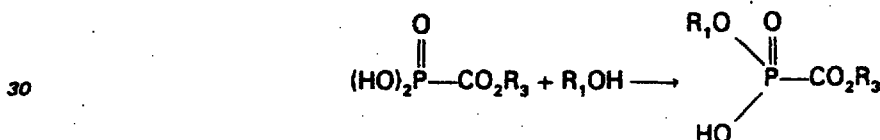
worin R_1 und R_3 die obige Bedeutung haben und R_{12} eine hydrolysierbare Phosphatestergruppe ist, oder

L. wäßrige Hydrolyse eines Hydroxycarbonylphosphonsäuretriesters, der eine silylveresterte Phosphonatgruppe enthält, nach der Gleichung



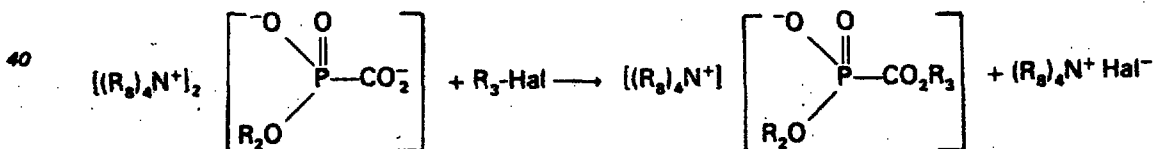
worin R_2 und R_3 die obige Bedeutung haben und R_6 ein inerte organischer Rest, vorzugsweise eine organische Gruppe, wie beispielsweise CH_3 , ist, oder

M. Umsetzung eines Hydroxycarbonylphosphonsäuremonocarbonsäureesters nach der Gleichung



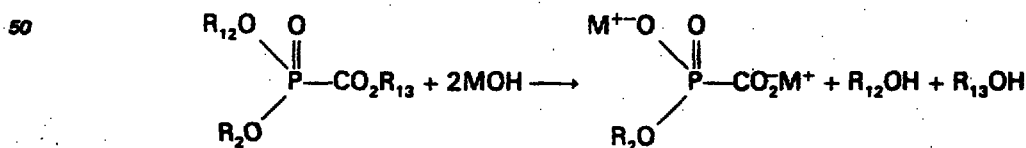
worin R_1 und R_3 die obige Bedeutung haben, oder

N. Umsetzung eines Hydroxycarbonylphosphonsäuremono-P-esters mit einem veresternden Halogenid unter Verwendung eines Tetraalkylammoniumsalzes als Katalysator nach der Gleichung



worin Hal Cl, Br oder I ist, R_2 und R_3 die obige Bedeutung haben und R_6 eine Alkylgruppe, wie beispielsweise n-Butyl, n-Pentyl, n-Hexyl, n-Heptyl oder n-Octyl, ist, oder

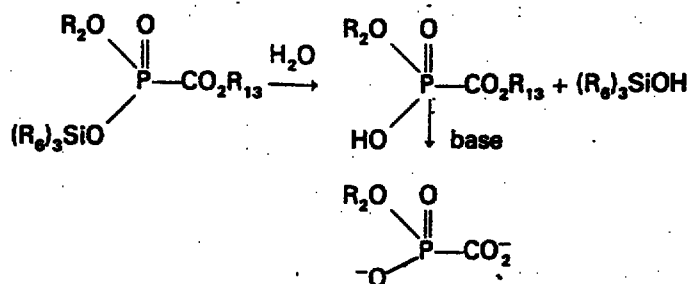
O. Hydrolyse eines Hydroxycarbonylphosphonsäuretriesters nach der Gleichung



worin M ein Kation, wie NH_4^+ oder Li^+ , Na^+ oder K^+ , ist, R_2 und R_{12} die obige Bedeutung haben, R_{13} die für R_{12} angegebene Bedeutung hat und R_{12} und R_{13} gleich oder verschieden sein können, oder

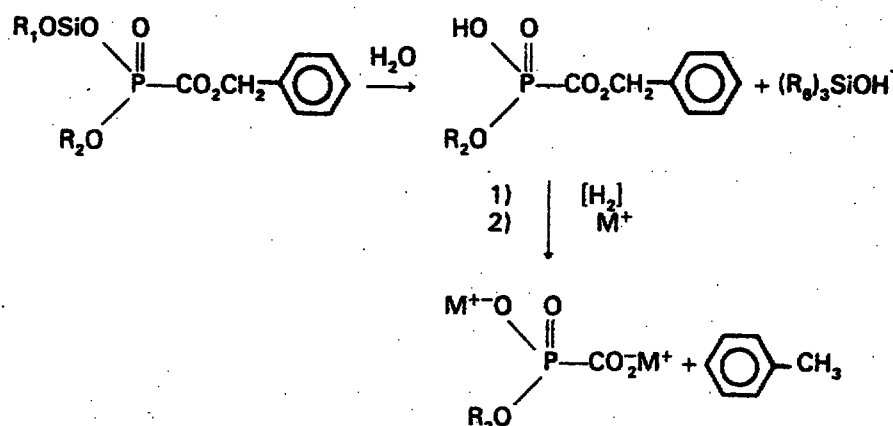
P. stufenweise Entesterung einer trisubstituierten Silylestergruppe am Phosphonsäurerest und der Carbonsäureestergruppe eines Hydroxycarbonylphosphonsäuretriesters nach der Gleichung





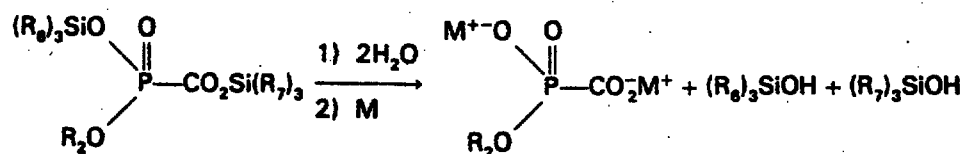
worin R_2 , R_6 und R_{13} die obige Bedeutung haben und die Silylestergruppe vorzugsweise eine Gruppe ist, wie sie beispielsweise oben in der Methode L genannt ist, oder

15 Q. stufenweise Entesterung der Silyl- und Benzylestergruppe eines Arylsilylbenzyloxycarbonylphosphonates nach der Gleichung



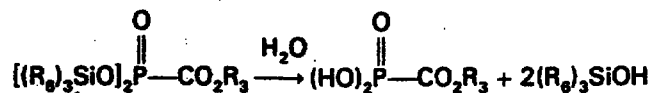
worin M^+ NH_4^+ oder ein Metall, wie beispielsweise Li^+ , Na^+ oder K^+ , ist und R_2 und R_6 die obige Bedeutung haben, oder

R. Entesterung der Bissilylestergruppen (an den Phosphonsäure- und an den Carbonsäuregruppen) eines Hydroxycarbonylphosphonsäuretriesters nach der Gleichung



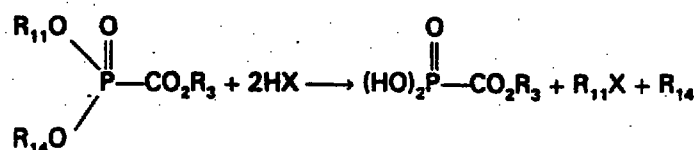
worin R_2 die obige Bedeutung hat, R_6 und R_7 inerte organische Reste sind, die gleich oder verschieden sind und vorzugsweise gleich sind und eine Gruppe, wie beispielsweise CH_3 bedeuten, oder

S. wäßrige Hydrolyse eines Hydroxycarbonylphosphonsäuretriesters, der zwei Phosphonsäuresilylestergruppen hat, nach der Gleichung



worin R_3 und R_6 die obige Bedeutung haben,

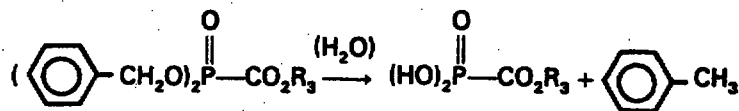
T. Umsetzung eines Triesters von Hydroxycarbonylphosphonsäure mit einer Halogenwasserstoffsäure nach der Gleichung



worin R_3 , R_{11} und R_{14} die obige Bedeutung haben und X Cl, Br oder I ist, oder

U. Hydrierung eines Dibenzylaryloxycarbonylphosphonates nach der Gleichung

5



10 worin R_3 die obige Bedeutung hat, oder

V. Umsetzung von Hydroxycarbonylphosphonsäure mit einem veresternden halogenid unter Verwendung eines Tetraalkylammoniumsalzes als Katalysator nach der Gleichung

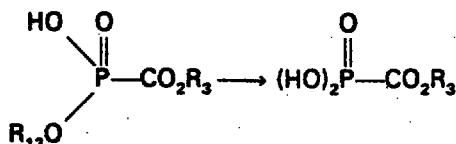
15



worin Hal Cl, Br oder I ist, R_3 die obige Bedeutung hat und R_8 eine Alkylgruppe, wie beispielsweise n-Butyl, n-Pentyl, n-Hexyl, n-Heptyl oder n-Octyl ist, oder

20 W. Umsetzung eines Hydroxycarbonylphosphonsäurediesters nach der Gleichung

25



worin R_3 und R_{12} die obige Bedeutung haben,

30 wonach die so erhaltene Verbindung der Formel I gegebenenfalls in ein physiologisch verträgliches Salz umgewandelt und/oder in ihre optische Isomeren aufgetrennt wird.

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