COMMONWEALTH of AUSTRALIA
PATENTS ACT 1952
APPLICATION FOR A STANDARD PATENT

We
RHONE-POULENC AGROCHIMIE
a French body corporate,
of 14-20, Rue Pierre Baizet,
Lyon 9E, France

hereby apply for the grant of a Standard Patent for an invention entitled:

"PHOSPHONIC ACID DIESTERS"

which is described in the accompanying specification.

Details of basic application(s):—

Number Convention Country Date
84 02968 FRANCE 23 February 1984

The address for service is care of DAVIES & COLLISON, Patent Attorneys, AMP Building, Hobart Place, Canberra, in the Australian Capital Territory, Commonwealth of Australia.

Dated this 30th day of January 1985.

To: THE COMMISSIONER OF PATENTS

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

The present invention relates to a process
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-1973
DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT
OR PATENT OF ADDITION

In support of the Application made for a patent
entitled: "PHOSPHONIC ACID DIESTERS"

I, Charles BRACHOTTE, Executive
of: RHONE-POULENC AGROCHIMIE, a French Body Corporate,
of: 14-20, Rue Pierre Baizet, Lyon 9e, France,
do solemnly and sincerely declare as follows:

1. (a) I am the applicant(x)(x), and I am authorized by

RHONE-POULENC AGROCHIMIE

the applicant(s) ....... for the patent application to make this declaration on its behalf.
or (b) I am authorized by

GUY LACROIX, a French Citizen of: 332 F - Balmont
La Duchere, 69009 Lyon, France.

2. (a) I am the inventor(x)(x) whose name is to appear in the application as defined

by Section 141 of the Act

or (b) I am a company or person(s) who are the inventor(s), insert full

name(s) and address(es) of inventor(s).

State manner in which applicant(s) discovered the invention and the facts upon which the applicant(s)
is entitled to make the application are as follows:

"The applicant would, if a patent were granted upon
an application made by the inventor, be entitled to
have the patent assigned to it".

3. The basic application........... as defined by Section 141 of the Act was made

in: FRANCE: NO. 840298 on the 23rd February, 1984

by RHONE-POULENC AGROCHIMIE

in the following manner:

AS THE FIRST APPLICATION....... made in a Convention country in respect of the invention the subject
of the application.

Declared at Lyon this 13th day of February, 1985.

DAVIES & COLLISON, MELBOURNE and CANBERRA.
DOCUMENTS LODGED WITH THIS APPLICATION ARE UNSUITABLE FOR REPRODUCTION AND MAY BE INSPECTED AT THE PATENT OFFICE A.C.T.
1. A process for the preparation of phosphonic acid diesters having the formula:

\[
\begin{align*}
0 &= \text{R} - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CO} - \text{OH} \\
&\quad \text{OR}^1
\end{align*}
\]

in which

- \text{R} represents a hydrogenolysable group, preferably an aralkyl group, and
- \text{R}^1 represents a hydrolysable group, wherein a phosphonic acid ester of the formula \((\text{R}^1\text{O})_2\text{P(O)H}\) is reacted with formaldehyde and a compound of the formula \(\text{R-NH-CH}_2\text{-COOH}\), \text{R} and \text{R}^1 having the meanings given above.
The following statement is a full description of this invention, including the best method of performing it known to us:

- 1 -
The present invention relates to a process for the preparation of N-substituted phosphonic acid esters of the N-phosphonomethylglycine family which may be used for the synthesis of herbicides.


One object of the invention is to provide a very simple and improved process for preparing herbicides, which employs relatively simple reactants, particularly glycine and its simple derivatives.

Other objects and advantages of the invention will become apparent in the course of the description which follows.

Mention has already been made (French Patent 2,129,327) of the formation of triesters of N-phosphono-methylglycine by the reaction of ethyl glycinate with formaldehyde and with diethyl phosphite. This process is unsatisfactory, since it is considered to be excessively directed towards the formation of N,N-bis-(phosphonomethyl)glycine. For this reason it has been proposed (French Patent 2,193,830) to prepare N-phosphono-methylglycine by reacting an N-arylalkylglycine with formaldehyde and phosphorous
acid, with subsequent elimination of the N-arylalkyl group by the action of hydrobromic or hydroiodic acid. However, this process is not considered to be satisfactory either, because of the low yields obtained and because of the formation of lachrymatory benzyl bromide. It has therefore been proposed to prepare N-phosphonomethylglycine by the reaction of N-substituted glycine with formaldehyde and with phosphorous acid, followed by a hydrogenolysis of the (N,N-disubstituted) N-phosphonomethylglycine which is obtained. This process has the disadvantage of being carried out in a very dilute medium and of being very lengthy. Also, more recently (European Patent 81,459) there has been a move towards reactants other than glycine and formaldehyde, and aminomethylphosphonic acid has been reacted with glyoxal in the presence of SO₂.

It has now been found, and this is the subject of the present invention, that herbicides of the N-phosphonomethylglycine family can be obtained by virtue of new intermediate products, which are themselves accessible from N-substituted glycine derivatives and formaldehyde.

The present invention relates to a process for the preparation of phosphonic acid diesters of the formula:
in which

\[
\frac{\text{OR}}{\text{R}} = \frac{\text{OR}}{\text{R}} \quad \text{OR}^1 \quad \text{R} \quad \text{OH} (\text{I})
\]

\[
\text{OR}^1 \quad \text{R} \quad \text{OH}
\]

\[
\frac{\text{OR}}{\text{R}} = \frac{\text{OR}}{\text{R}} \quad \text{OR}^1
\]

R represents a hydrogenolysable group,
preferably an aralkyl group and
\( R^1 \) represents a hydrolysable group.

The radical \( R \) may, in particular, be a
radical of the formula:

\[
\frac{\text{R}^4}{\text{Ar} - \text{C} - \text{R}^3}
\]

in which

\( \text{Ar} \) is an aromatic group, preferably aryl and more particularly phenyl; this radical \( \text{Ar} \) may, if desired, carry one or more substituents which do not interfere with the reactions involved in the process (alkyl, alkoxy, nitro and others, the number of carbon atoms being preferably equal to 6 at most), although it does not appear particularly advantageous to employ such substituents, and

\( R^3 \) and \( R^4 \) each represent a hydrogen atom or a radical \( \text{Ar} \) or an alkyl group, preferably having at most 20 6 carbon atoms.

Radicals \( R \) which may be mentioned are the benzyl, 1-phenylethyl, 1-phenylpropyl, naphthylmethyl,
1-naphthylethyl, 1-naphthylpropyl, diphenylmethyl and trityl (i.e. triphenylmethyl) radicals. Benzyl is preferred.

$R^1$ is a hydrolysable radical; examples of hydrolysable radicals which may be mentioned are optionally substituted hydrocarbyl radicals, particularly alkyl or phenyl radicals which are optionally substituted by halogen atoms or by phenyl, cyano, alkoxy or alkoxy carbonyl groups. $R^1$ generally contains at most 12 carbon atoms and is advantageously an alkyl radical containing from 1 to 6 carbon atoms or a phenyl radical.

The process for the preparation of the compounds of formula (I) is carried out by the reaction of a phosphite (or phosphonic acid ester) of the formula:

$$\begin{align*}
0 - R^1 \\
0 &= P - H \\
0 &= R^1
\end{align*}$$

(III)

when $R^1$ is as hereinbefore defined, with formaldehyde and an N-substituted glycine derivative, the substituent on the nitrogen atom being a hydrogenolysable substituent; this N-substituted glycine derivative is in practice a compound of the formula $R-NH-CH_2-CO-OH$. 


The reaction is generally carried out at between 0 and 100°C, preferably between 1 and 90°C, by simply mixing the reactants. Although a large excess (3/1 to 1/3 in molar ratios) of one of the reactants relative to the other is possible, it is in practice more advantageous to operate as close to stoichiometry as possible and not to depart by more than 20 mole % from this stoichiometry. It is indeed one of the major advantages of the invention that it does not require an excess of one of the reactants relative to the others. Another advantage of the invention lies in the good yields obtained in the preparation of the compounds according to the invention.

Formaldehyde is employed in any of the conveniently accessible forms. According to a most commonly used method it is employed in the form of an aqueous solution of a concentration between 1% and saturation, preferably of 30% to 40%.

The reaction may be carried out in the presence of an inert solvent; sometimes such a solvent serves no purpose but the reaction mixture usually contains water, especially because of the use of formaldehyde in an aqueous solution.

The reaction product is isolated by any means known per se.

The products of the formula (I) may be converted into known herbicidal products of the
wherein $R^1$ is as hereinbefore defined,

by simple hydrogenolysis of the group $R$. In most cases

this is a debenzylation. It is carried out

advantageously in an aqueous or alcoholic medium at

ambient or elevated temperature, and at atmospheric

pressure or above. The usual catalysts of

hydrogenolysis of the radicals $R$ in question may be

employed as a catalyst. Suitable catalysts which may be

mentioned are palladium, platinum, and Raney nickel.

This catalyst may be employed with or without an inert

support. It is also possible to employ the

abovementioned metals, particularly palladium and

platinum, in the form of salts, hydroxides, or oxides,

which are converted to the corresponding metal under

the action of hydrogen. Palladium-based catalysts,

such as palladium on charcoal or palladium on barium

sulphate, or palladium hydroxide on charcoal, are

employed as a preferred debenzylation catalyst. At the

end of the reaction, the catalyst may be separated by

filtration and the filtrate evaporated; this yields the

product of the formula (IV) in a practically pure
state. A major advantage of the invention lies in the fact that the reaction time for this debenzyla-
tion is relatively short, which makes it possible to use reduced quantities of catalyst.

When it is desired to prepare known non-esterified forms of herbicides, such as for example N-phosphonomethylglycine itself, the product of the formula (IV) may be hydrolysed completely or partially in a known manner, e.g. by heating with an aqueous solution of an acid or alkaline agent, particularly a hydroxide or carbonate of an alkali metal or alkaline-earth metal, or hydrochloric, sulphuric, phosphoric, perchloric or arylsulphonic acids. This hydrolysis may also be accompanied by a salt formation or a conversion to other herbicidal derivatives. This hydrogenolysis can also be followed by a hydrolysis and/or a salt formation reaction.
The examples which follow and which are given without implying a limitation illustrate the invention and show how it can be put into practice.

Example 1

N-Benzylglycine (39 g), water (80 ml) and an aqueous solution (20.3 ml) of formaldehyde (0.248 mole) are mixed. Diphenylphosphite (C₆H₅O)₂PH(0) (58 g = 0.248 mole) is added dropwise at ambient temperature. After 30 minutes, the temperature is allowed to rise to 30° and stirring is continued for one hour. The product is filtered off, washed with water and dried. After recrystallisation from a mixture of isopropyl ether and isopropanol in the ratio of 10/1 by volume, a white powder (57.4 g) is obtained (yield 59.1%), which melts at 91°C and consists of the product of the formula:

\[ \text{C}_6\text{H}_5\text{O} \quad \text{CH}_2\text{C}_6\text{H}_5 \]
\[ 0 = \text{P} - \text{CH}_2 \quad \text{N} - \text{CH}_2 - \text{COOH} \quad (V) \]

Example 2:

N-Benzylglycine (16.5 g), water (28 ml) and diethylphosphite (C₂H₅O)₂PH(0) (13.8 g) are mixed. An aqueous 37% strength formaldehyde solution (9 ml = 0.11 mole) is added at 20°C. No exothermic
effect is observed. The mixture is heated for five hours at 50° and then cooled, and CH₂Cl₂ (40 ml) is added. The organic phase is separated off and water (40 ml) followed by N aqueous NaOH solution (100 ml) are added. The aqueous phase is decanted, extracted with CH₂Cl₂ and acidified. The organic phase is dried and evaporated. A product (23.5 g = 74% yield) is obtained of the formula:

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \quad \frac{\text{CH}_2 \cdot \text{C}_6\text{H}_5}{\text{O} = \text{P} - \text{CH}_2 \cdot \text{N} - \text{CH}_2 \cdot \text{COOH}} \\
\text{C}_2\text{H}_5\text{O} &
\end{align*}
\]  

Example 3:
Ethyl N-benzylglycinate is saponified in situ. An aqueous 30% strength NaOH solution (0.5 l = 5 moles) and water (1 l) are mixed into this solution, ethyl N-benzylglycinate (965 g) is poured gradually over one hour. The temperature rises to 45°C. The ethanol is distilled off, the residue is cooled and a 6 N aqueous hydrochloric acid solution (0.82 l) is added. The N-benzylglycine precipitates. Diethylphosphite (690 g) and 37% strength aqueous formaldehyde (0.45 l = 5 moles) are added. The mixture is heated for 5 hours 30 minutes at 50°C. Thereafter, the procedure of Example 2 is followed. The product of formula (VI) (116 g = 71% yield) is obtained.
CLAIMS
The claims defining the invention are as follows:

1. A process for the preparation of phosphonic acid diesters having the formula:

\[
\begin{align*}
\text{OR}^1 & \quad \text{R} \\
0 &= \text{P} - \text{CH}_2 - \text{N} - \text{CO} - \text{OH} \\
\text{OR}^1
\end{align*}
\]  

(1)

in which

- \text{R} represents a hydrogenolysable group, preferably an aralkyl group, and
- \text{R}^1 represents a hydrolysable group, wherein a phosphonic acid ester of the formula \((\text{R}^1\text{O})_2\text{P(O)H}\) is reacted with formaldehyde and a compound of the formula \(\text{R-NH-CH}_2-\text{COOH}\), \text{R} and \text{R}^1 having the meanings given above.

2. A process according to claim 1, wherein the radical \text{R} is a radical of the formula:

\[
\begin{align*}
\text{R}^4 & \quad \text{R}^3 \\
\text{Ar} - \text{C} & \\
\text{R}^3
\end{align*}
\]  

(II)

in which

- \text{Ar} is an aromatic group, preferably aryl, which is optionally substituted and
- \text{R}^3 and \text{R}^4 each represent a hydrogen atom or a radical \text{Ar} or an alkyl group, preferably having at most
6 carbon atoms.

3. Process according to claim 2, in which R is the benzyl radical.

4. Process according to any one of claims 1 to 3, in which R is an alkyl or phenyl radical which is optionally substituted and has at most 12 carbon atoms.

5. Process according to any one of claims 1 to 4, in which R is an alkyl radical having from 1 to 6 carbon atoms or is the phenyl radical.

6. Process according to any one of claims 1 to 5, wherein the reaction is carried out between 0 and 100°C, each reactant being present in a proportion which does not differ by more than 20% from stoichiometry.

7. Process according to any one of claims 1 to 6, wherein the reaction is carried out in an aqueous medium.

8. Process according to claim 1 substantially as hereinbefore described.

9. Process according to claim 1 substantially as hereinbefore described in any one of Examples 1 to 3.

10. A compound of general formula (I) wherein R and R are as defined in claim 1 when prepared by a process claimed in any one of claims 1 to 9.
11. Process for the preparation of compounds of the formula:

\[ \text{OR} \]

\[ \text{OR} \]

\[ \text{O} = \text{P} - \text{CH}_2 - \text{NH} - \text{CH}_2 - \text{CO} - \text{OH} \]  \hspace{1cm} (IV)

\[ \text{OR} \]

wherein \( R^1 \) is as defined in claim 1 which comprises the hydrogenolysis of a compound of formula (I) prepared by a process according to any one of claims 1 to 9.

12. Process according to claim 11, wherein the said process is followed by a hydrolysis and/or a salt-forming reaction.

13. Process according to claim 11 substantially as hereinbefore described.

14. A compound of general formula (IV) wherein \( R^1 \) is as defined in claim 1, when prepared by a process according to claim 11 or 13.

15. A compound of formula (I) wherein \( R \) and \( R^1 \) are as defined in claim 1.

16. The compound of formula (I) wherein each of the symbols \( R^1 \) represents phenyl and \( R \) represents benzyl.

17. The compound of formula (I) wherein each of the symbols \( R^1 \) represents ethyl and \( R \) represents benzyl.
18. The parts, elements, steps and features referred to or indicated in the specification and/or claims of this application, individually or collectively and any and all combinations of any two or more of said parts, elements, steps or features.

DATED this 30th day of January 1985.

RHÔNE-POULENC AGROCHIMIE

By its Patent Attorneys

DAVIES & COLLISON
N-arylalkylglycine with formaldehyde and phosphorous