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What are the Requirements in the Glyphosate Molecule in Order for it to be Herbicidally Active?*

Ludwig Maier

Novartis International Inc., CH-4002 Basel, Switzerland

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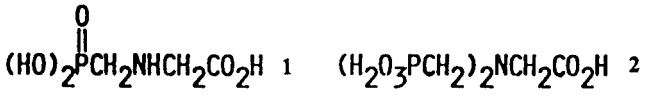
ABSTRACT: *An attempt has been made to determine what the requirements are for the Glyphosate molecule to be herbicidally active, and also to determine whether the optimum of biological activity has been achieved with the Glyphosate structure. In order to obtain the answers to these questions, we have segmented the Glyphosate molecule into five sections and then changed each section to determine the biological activity of each new molecule so produced.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:454–469, 2000

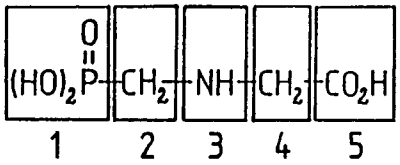
INTRODUCTION

In the past 25 years, *N*-phosphonomethylglycines have been investigated extensively, since some of these compounds such as Glyphosate (**1**) and Glyphosine (**2**) exhibit herbicidal and plant growth regulating properties [1].



Several processes have been developed for the preparation of these compounds [1]. Some of them are shown in Scheme 1.

What are the requirements for the Glyphosate molecule in order for it to be herbicidally active, and is the optimum of the biological activity reached with the Glyphosate structure? To answer this question we have segmented the Glyphosate molecule into five sections and then changed each section and determined the biological activity of the compounds obtained.



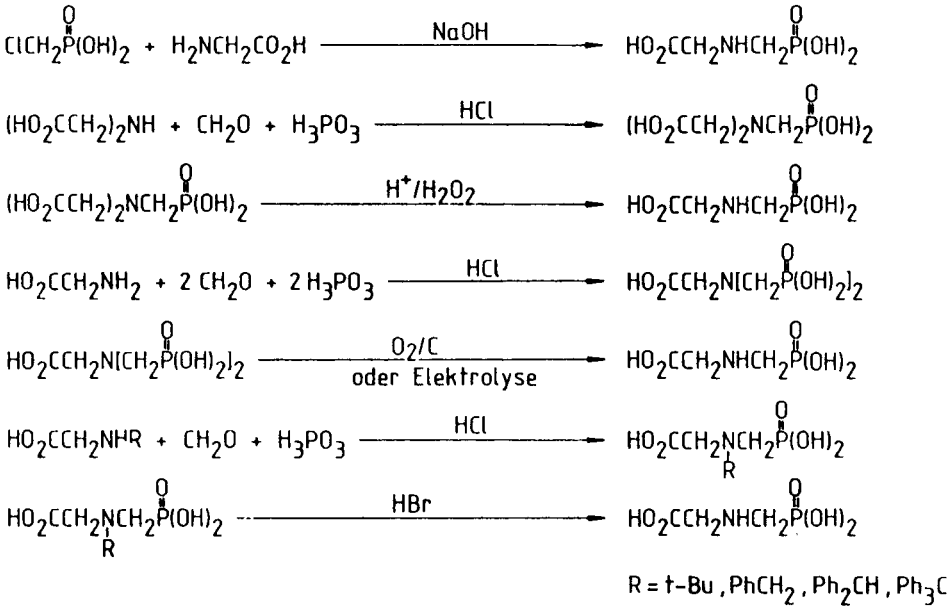
Let us start with section 1. We have tried to substitute one or both OH-groups on phosphorus by other groups and then see the effect on the biological activity.

RESULTS AND DISCUSSION

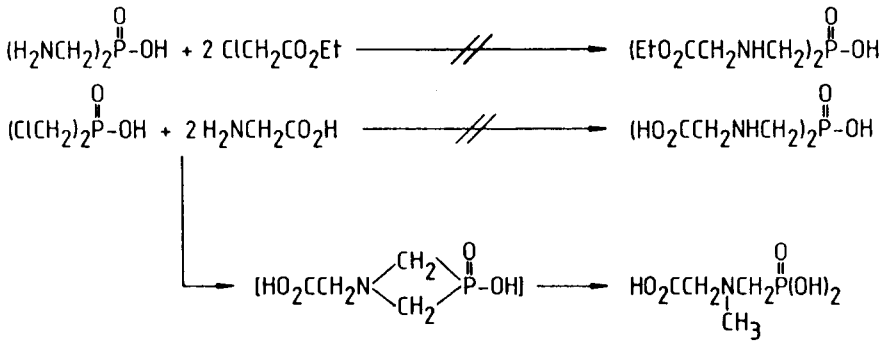
Attempts to prepare bis(*N*-glycinomethyl)phosphinic acid in a similar way as Glyphosate were not successful. Thus, in the reaction of bis(chloromethyl) phosphinic acid with glycine in the presence of NaOH, the desired phosphinic acid was not obtained; instead *N*-methyl-*N*-phosphonomethylglycine was formed [2]. The formation of this phosphonic acid has been explained by assuming that the four-membered ring formed as an intermediate is hydrolyzed (Scheme 2).

Also bis(aminomethyl)phosphinic acid [3] did not react with chloroacetic acid in the desired way.

*Extended version of a lecture given at the XIVth ICPC in Cincinnati, Ohio, July 1998.



SCHEME 1



SCHEME 2

Some time ago, we reported on the Mannich-type reaction of hypophosphorous acid with formaldehyde and secondary amines in strongly acidic solution to give bis(dialkyl-aminomethyl)phosphinic acids [4].

This reaction can also be successfully carried out with functionally substituted amines [5]. In order to obtain good yields, it is necessary to carry out the reaction under an atmosphere of nitrogen to avoid oxidation and also to keep the pH of the solution acidic. As functionally substituted amines, we have used iminodiacetic acid and benzylglycine [5] (Scheme 3).

Both acids (**3**,**4**) are obtained as monohydrochlorides. Apparently only the phosphinic acid proton is acidic enough to form a betaine; the second amine-nitrogen is protonated by HCl.

Attempts to oxidize **3** with oxygen according to a process used for the preparation of Glyphosate was not successful. When bis[di(hydroxycarbonylmethylaminomethyl)]-phosphinic acid **3** was treated with O_2 at 2–3 atm. and 90–110°C in the presence of carbon black as a catalyst, a mixture was obtained in which only traces of bis(*N*-glycinomethyl) phosphinic acid **5** were detected by ^{31}P NMR.

However it was found that the benzyl derivative **4** could be debenzylated at room temperature in good yields with H_2 at normal pressure in the presence of 5% Pd on carbon using water/acetic acid or H_2O/C_2H_5OH as the reaction medium to give **5**[5]. One of the questions that arose from this work was the following: does H_3PO_2 first react with formaldehyde and then condense with benzylglycine or is an *N*-hydroxymethyl-*N*-benzylglycine formed first, which then condenses with H_3PO_2 with elimination of water? To answer this question, we prepared hy-

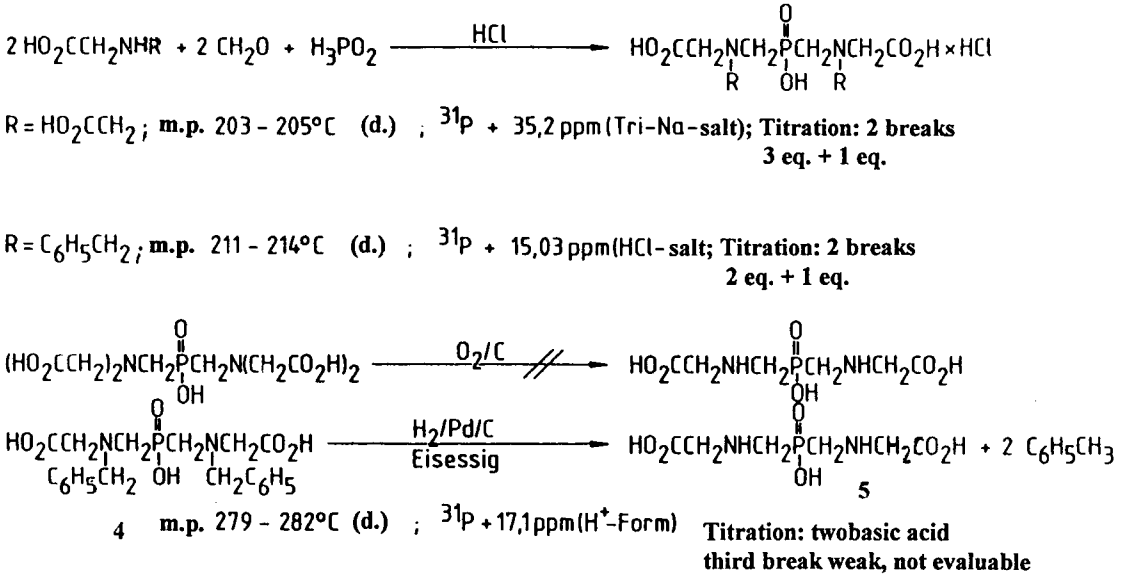
droxymethyl-phosphonous acid **6** by the reaction of one equivalent of formaldehyde with H_3PO_2 in over 80% yield [6] (Scheme 4).

The acid **6** suffers a fast P–H/P–D exchange when dissolved in D_2O as is clearly seen in the ^{31}P NMR spectrum.

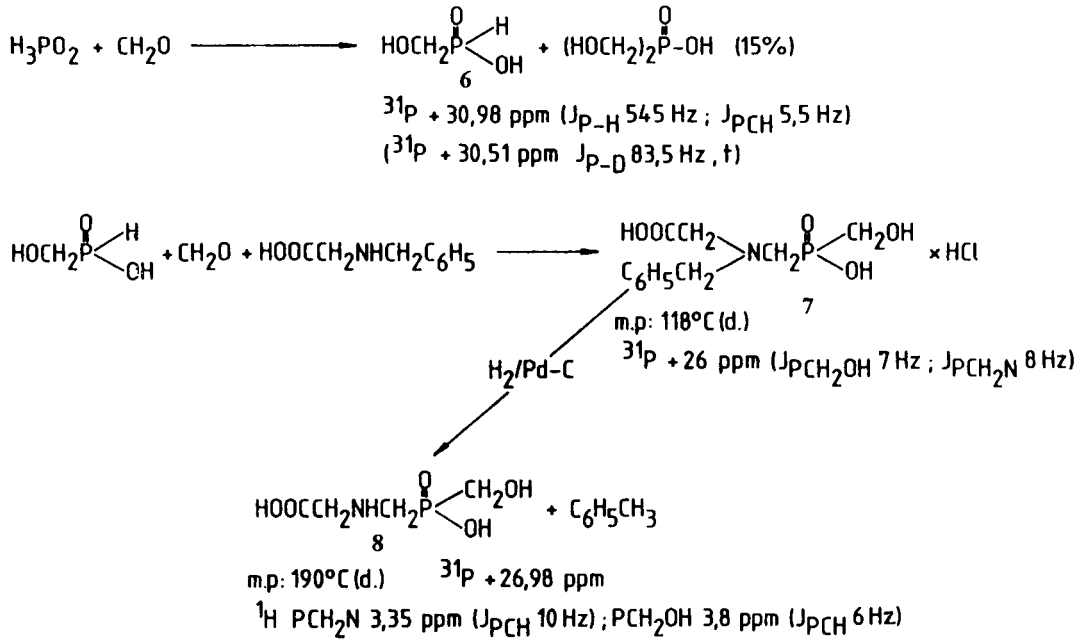
No reaction occurred when **6** was treated with *N*-benzylglycine. Furthermore, when hydroxymethylphosphonous acid was caused to interact with formaldehyde and *N*-benzylglycine, the hydroxymethyl-*N*-benzyl-*N*-glycinomethylphosphinic acid **7** was obtained in 88% yield (Scheme 4).

Thus, it is clear that the reaction proceeds by the interaction of a P–H bond with *N*-hydroxymethyl-*N*-benzylglycine.

The benzyl derivative can easily be debenzylated



SCHEME 3



SCHEME 4

with H_2 in the presence of 5% Pd/C in aqueous solution to give hydroxymethyl-*N*-glycinomethylphosphinic acid **8** as a crystalline solid of m.p. 190° (dec.) [6] (Scheme 4).

Instead of phosphonous acids, alkylphosphonous dihalides may be used in this Mannich-type reaction [6]. As it is well known, these compounds react with water with the formation of phosphonous acids (Scheme 5).

Attempts to prepare trifluoromethyl-*N*-glycinomethylphosphinic acid from trifluoromethyl-chloromethylphosphinate and glycine failed. Only Glyphosate was obtained [7].

Whereas the alkylsubstituted phosphinic acids **9** are obtained as hydrochlorides, the Cl_3C-, $ClCH_2$-, and C_6H_5-derivatives **10** do not form hydrochlorides (Scheme 5). Apparently the electronegative substituents effect an increase of the acidity of the phosphinic acid proton, which makes it able to protonate the nitrogen, whereas the alkyl derivatives cannot do this, and therefore add hydrochloric acid [6].

2-Chloroethyldichlorophosphine and cyanomethyldichlorophosphine react differently. This will be discussed later.

Debenzylation with H_2 in the presence of Pd on carbon as a catalyst in acetic acid or alkohol/water is, with one exception, without problems (Scheme 6).

All phosphinic acid derivatives are obtained as crystalline white solids with high decomposition points. Even after recrystallization from water/acetone the ethyl, *n*-propyl, and tertiary butyl derivatives **11** are obtained as semihydrochlorides, whereas the other derivatives such as when $R = CH_3$, $ClCH_2$, Cl_2CH, Cl_3C, C_6H_5 **12** form no hydrochlorides (Scheme 6).

Very likely, all derivatives possess the betaine structure. This is also indicated by the strong dependence of the ^{31}P-chemical shift upon the pH.

The pure acid, 12, $R = CH_3$, dissolved in water, exhibits a pH of 2.8 and a ^{31}P-chemical shift of +30 ppm; at pH 1 (adjusted with HCl) apparently a hydrochloride is formed ($\delta^{31}P$ + 32,8 ppm) in solution (not stable in the crystalline state): at pH 8 the monosodium-salt ($\delta^{31}P$ + 35.6 ppm) and at pH 10 the disodium ($\delta^{31}P$ + 39.1 ppm) is formed.

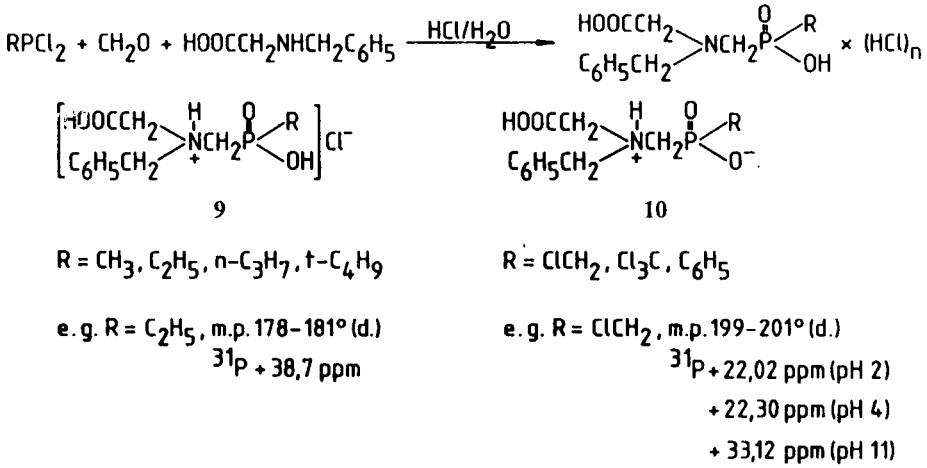
The debenzylation of the trichloromethyl derivative had to be carried out with stoichiometric amounts of hydrogen. Excess hydrogen and longer reaction periods led to a reductive elimination of one chlorine and produced a dichloromethyl group **13** (Scheme 7).

An attempt to oxidize bis(*N*-hydroxycarbonylmethyl)-aminomethyl-phenyl phosphinic acid **14** with oxygen under pressure at 90–110°C in the presence of carbon black as catalyst to *N*-glycinomethylphenylphosphinic acid **15** was not successful. Only decomposition products could be obtained.

On the other hand, a Japanese patent publication describes the oxidation of the corresponding methyl derivative **16** with H_2O_2 in sulfuric acid solution to give **17**. However, the m.p. given in the patent is not in agreement with that of our product. (Scheme 7).

The carboxylic acid groups of **5** (Scheme 8) and **11** and **12** (Scheme 9) are readily esterified [6] with alcohols in the presence of hydrogen chloride. Furthermore they form crystalline salts with amines [6] (Schemes 8 and 9).

The diester of **11**, $R = CH_3$ is obtained directly in the reaction of *O*-ethyl-methylphosphonite with *N*-ethoxycarbonylmethyl-hexahydrotriazine



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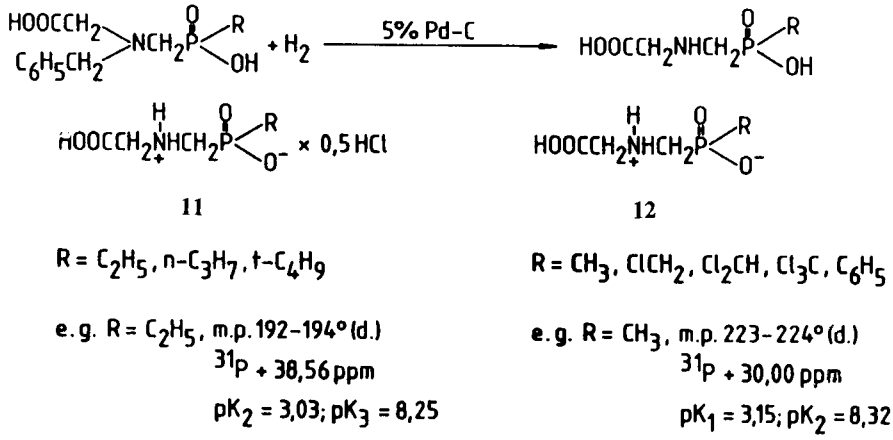

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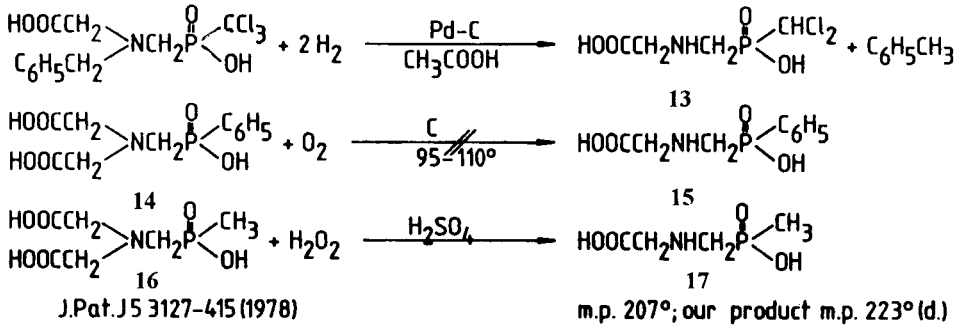
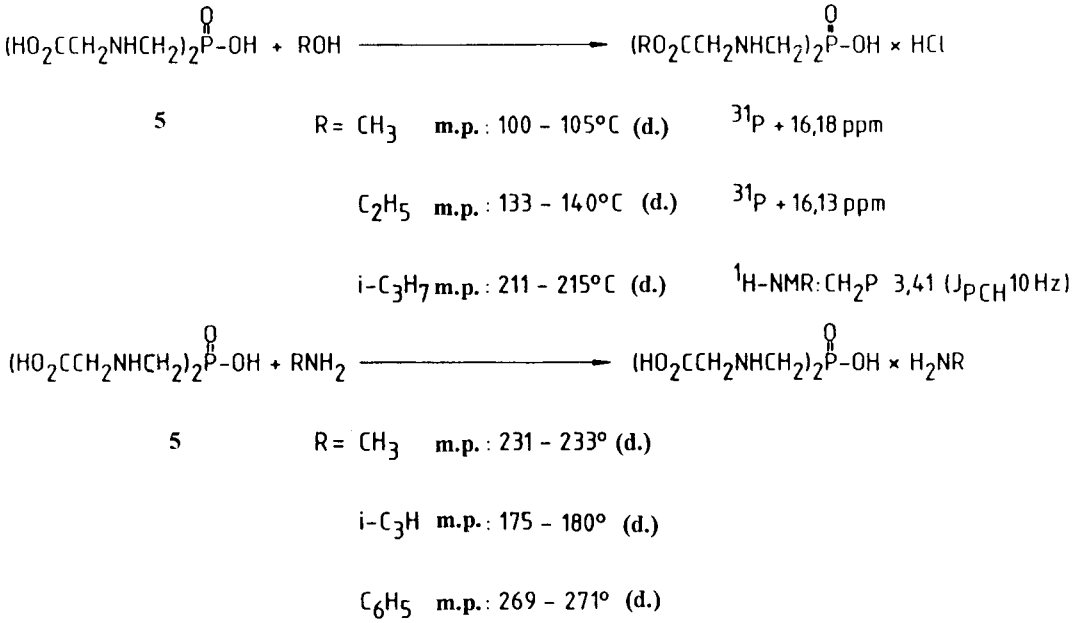
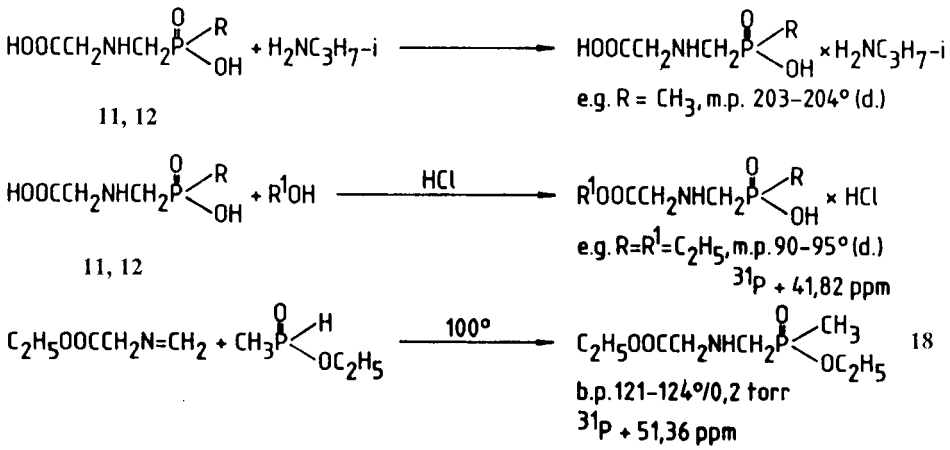


SCHEME 7



SCHEME 8



SCHEME 9

(Scheme 9). However, this ester **18** is not very stable and decomposes on standing at room temperature.

Now let me come back to the reaction of cyanomethylphosphonous and 2-chloroethylphosphonous dichloride with CH_2O and benzylglycine. Cyanomethylphosphonous dichloride **19** was prepared by the reaction of Bu_3SnCH_2CN with PCl_3 [8]. Previously, the synthesis of cyanomethyl-group containing phosphines from $LiCH_2CN$ and R_2 PCl had been described [9]. There is no indication in the literature whether this procedure would also work for the preparation of cyanomethylphosphonous dichloride **19**. Compound 19 is a waterclear liquid, b.p. 85–88°/15 torr and exhibits a ^{31}P-chemical shift of +159.7 ppm; thus the cyanomethyl group seems to deshield the phosphorus atom to the same extent as a phenyl group does (^{31}P chemical shift of $PhPCl_2$ is +161 ppm).

Reaction of cyanomethyldichlorophophine with formaldehyde and benzylglycine does not lead to the cyanomethylsubstituted phosphinic acid. Instead, under the reaction conditions, the cyanomethyl-group is hydrolyzed and *N*-benzyl-*N*-glycinomethyl-carboxymethylphosphinic acid **20** is formed in 40% yield (Scheme 10). Debenzylation with H_2/Pd/C yields *N*-glycinomethyl-carboxymethylphosphinic acid 21 in 71% yield as a high melting solid (dec. 187°C) (Scheme 10).

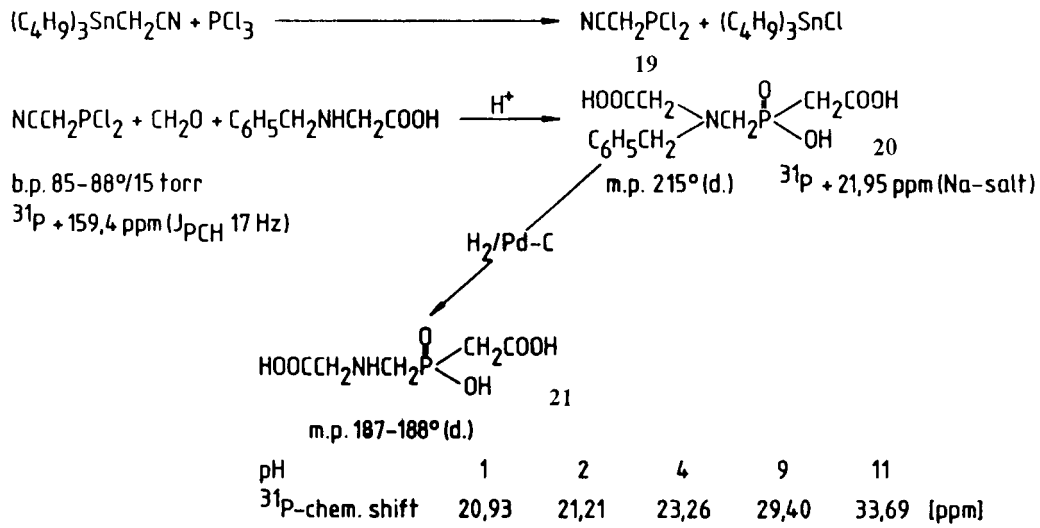
Reaction of 2-chloroethylphosphonous dichloride **22** with formaldehyde and benzylglycine does not yield the open chain phosphinic acid **23**. Instead, cyclization occurs and the eight-membered ring lactone, 4-benzyl-1,4,6-oxazaphosphocan-6-hydroxy-2,6-dioxide **24** is formed in over 80% yield [8] (Scheme 11).

Debenzylation with H_2 in the presence of Pd/C leaves the eight-membered ring intact and produces 1,4,6-oxazaphosphocan-6-hydroxy-2,6-dioxide **25** in 75% yield. The ^{31}P NMR signal lies in the region expected for phosphinic acids (+44.8 ppm) and the ^{1}H NMR spectrum shows the expected peaks. In the mass spectrum a molecular ion peak is observed.

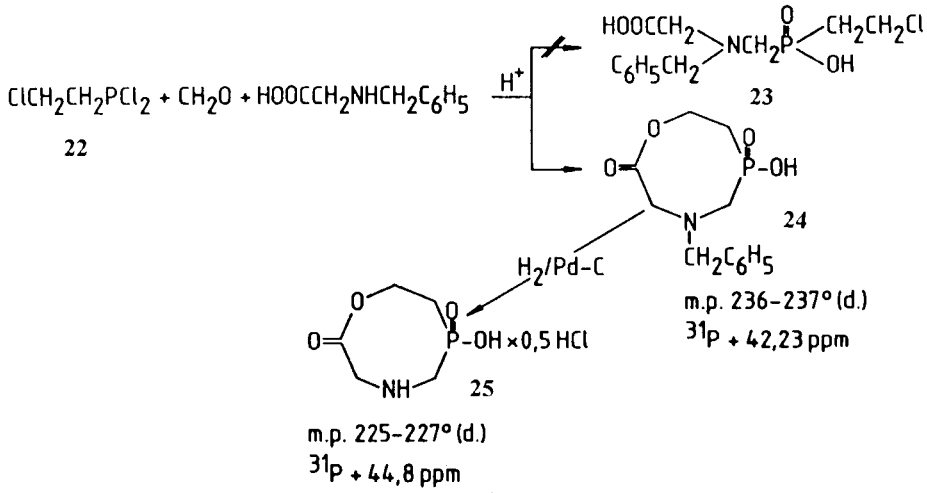
Also, the open chain phosphinic acid **26** was not formed in the reaction of *O*-ethyl-2-chloroethylphosphonite with the trimeric Schiff base from ethyl glycinate and formaldehyde (Scheme 12); instead, HCl was eliminated during the reaction and cyclization to the 1-ethoxycarbonylmethyl-1,3-azaphospholidin-3-ethoxy-3-oxide **27** occurred. This compound is a clear colorless liquid with a ^{31}P-chemical shift of +69.78 ppm and a molecular ion peak at 235 [8].

In another experiment, we observed that secondary phosphine oxides also add to the hexahydrotriazine [10] (Scheme 13). Thus, when sec. diethylphosphine oxide was heated with tris(*N*-ethoxylcarbonylmethyl)-hexahydrotriazine, a high yield of the corresponding phosphine oxide **28** was obtained, which on hydrolysis, gave a quantitative yield of *N*-glycinomethyl-diethylphosphine oxide **29** as a crystalline solid of m.p. 204°C [10]. The ^{1}H NMR spectra confirm the structures of these two compounds **28** and **29**. The *N*-glycino-methyl-dimethyl, -dipropyl-, and -dibutylphosphine oxides were similarly prepared [11].

All the compounds so far discussed showed a much weaker herbicidal activity than glyphosate; for example methyl-glycino-*N*-methylphosphinic acid **12**, R = CH_3, controls only some weeds at 4 kg/ha but not all as Glyphosate does. To get a better insight into the structure-activity relationship of this class of compounds, it seemed of interest to synthesize cyclic compounds that still contain the structural element of Glyphosate. I have already discussed cyclic compounds in which the ring was between units 1



SCHEME 10



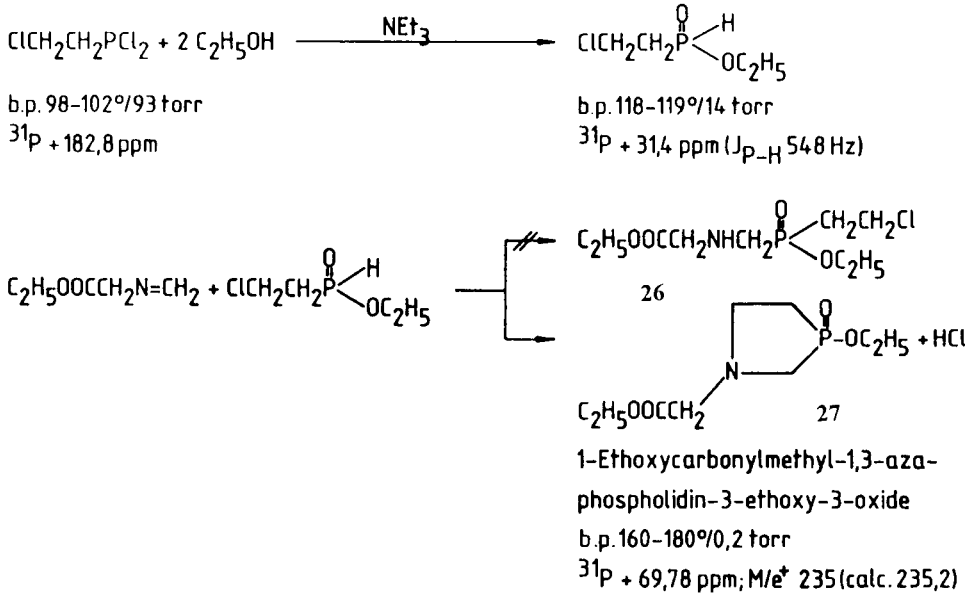
1,4,6-Oxazaphosphocan-2-oxo-6-hydroxy-6-oxide

SCHEME 11

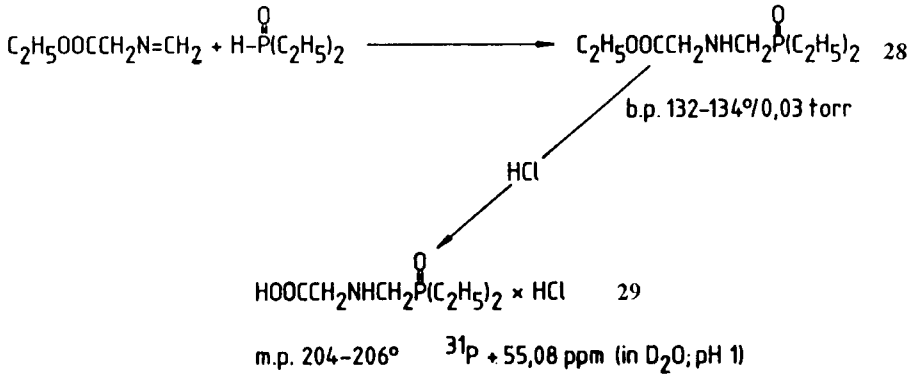
and 5 or 1 and 3 of Glyphosate. Now, cyclic compounds shall be described where the ring may be on carbon 2, between 2 and 3, 2 and 4, 3 and 4, or on 4. Finally, the unit 5 can be replaced by a carboxylic acid equivalent, as for example tetrazole. The ring on unit 2 is formed by double alkylation of **30** or **35** with 1,2-dibromoethane using NaH or LDA as base [12] (Scheme 14). Hydrolysis of the intermediate **31** and **36** with dilute HCl at 20°C yields 1-amino-cyclopropan-1-phosphonates **32**. 1-Amino-cyclopropane-1-phosphonic acid is formed when the hydrolysis is carried out with conc. HCl. Alkylation of **32** with bromoacetic acid ethyl ester in THF in the presence of *i*-Pr_2NEt produces **33**, which gives, on treatment with Me_3SiBr, 1-*N*-carbethoxymethyl-aminocyclopropane-1-phosphonic acid **34** [12] (Scheme 14).

The ring between 2 and 3 is synthesized by addition of sec. phosphites to the 1-pyrroline-trimer **37** to give **38** [12] followed by alkylation with bromoacetate to produce **39** (Scheme 15). Hydrolysis with conc. HCl yields 2-dihydroxyphosphonyl-*N*-caboxymethylpyrrolidine **40** in 40% yield [12].

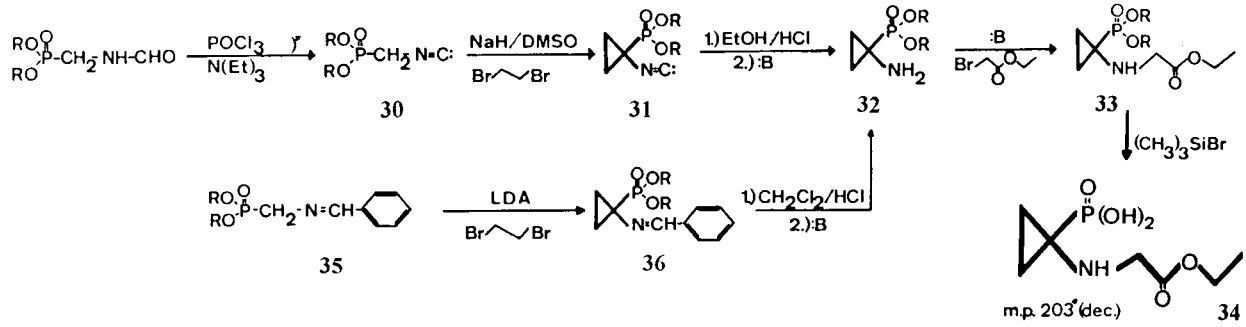
The five-membered ring between 2 and 4 was constructed by heating 1-pyrroline-5-butoxycarbonyl trimer **41** with diethyl phosphite to give **42** [11] (Scheme 16). Hydrolysis with conc. HCl gave



SCHEME 12



SCHEME 13



SCHEME 14

the acid **43** as an oil, which gave however, a crystalline cyclohexylamine salt **43** (Scheme 16).

Shono's procedure [13] for the formation of P–C bonds was successfully applied in the synthesis of a six-membered ring between unit 2 and 4, i.e., 2-carboxy-6-dihydroxyphosphonyl-piperidine **46** [12] (Scheme 17). This involved treatment of N-fomyl-2-carbethoxy-6-methoxy-piperidine **44** with triethyl phosphite in the presence of $BF_3.Et_2O$ to give **45** followed by hydrolysis with conc. HCl.

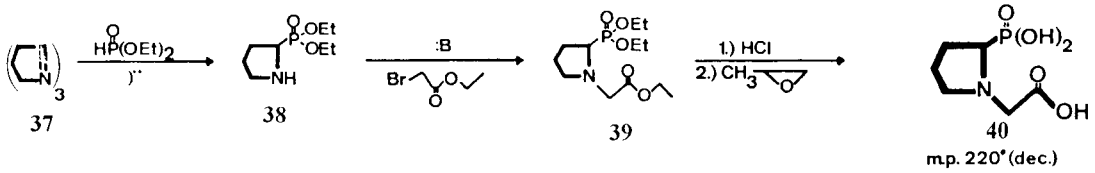
The Mannich reaction is well suited for the synthesis of compounds that contain the ring between unit 3 and 4 [12] (Scheme 18). For this purpose, proline or piperidine-2-caboxylic acid are heated with CH_2O and H_3PO_3 in acidic solution. Both acids **47** and **48** are obtained in good yield and high purity [12].

Two examples are given for compounds which contain the ring on unit 4. The first involves addition of diethyl phosphite to the Schiff base of aminocyclopropylcarboxylate to give **49** [12] (Scheme 19).

Depending on the conditions used, hydrolysis of **49** yields **50, 51**, or **52**, respectively.

The synthesis of the second example, that is, 1-*N*-phosphonylethyl-aminocyclohexane-1-carboxylic acid **54** involved reaction of cyclohexanoncyanohydrin with aminomethylphosphonate to give the ester **53** which, on hydrolysis with conc. HCl, yields crystalline **54** [12] (Scheme 20). All cyclic Glyphosate derivatives showed no herbicidal activity.

I have not yet said much about the requirements on nitrogen (section **3** of Glyphosate molecule). The preparation of Glyphosate made use of *N*-phosphonylmethyl-*N*-benzylglycine, *N,N*-bis(phosphonylmethyl)glycine and *N*-phosphonylmethyl-iminodi(acetic acid) as starting materials. All these



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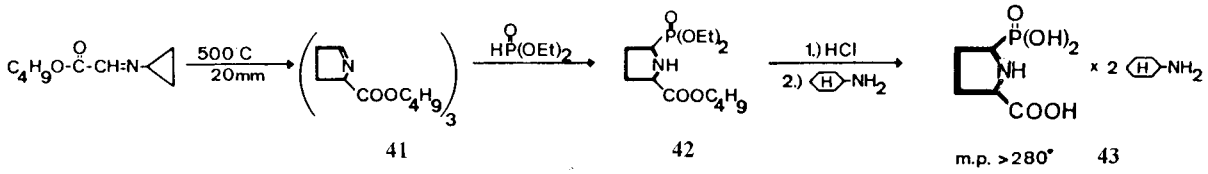
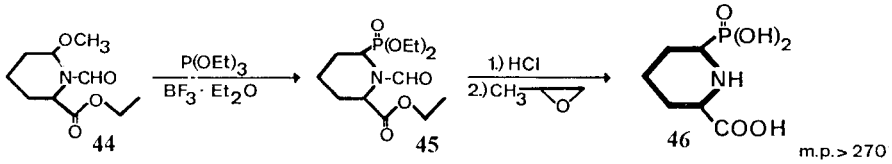
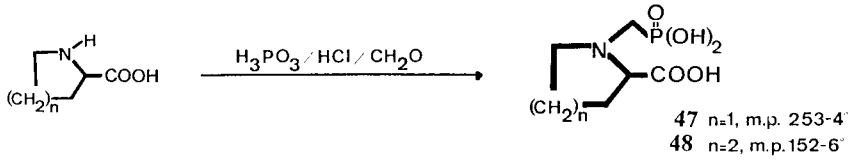


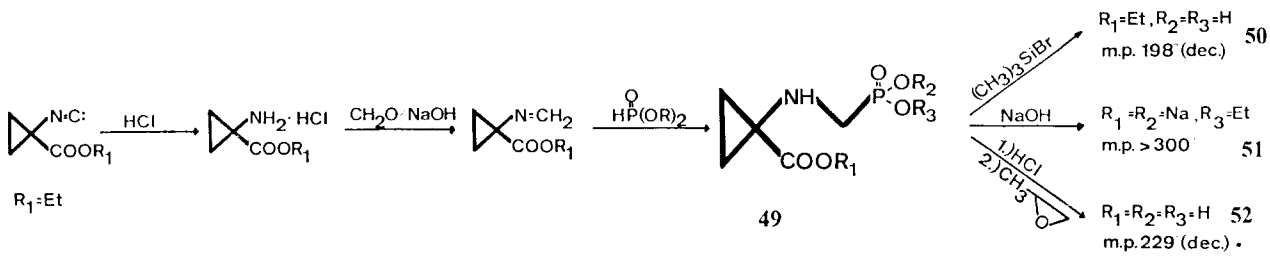
SCHEME 16



SCHEME 17



SCHEME 18



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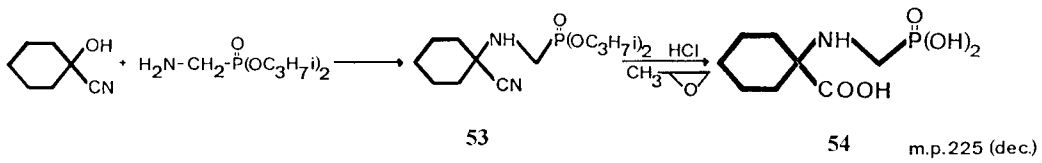
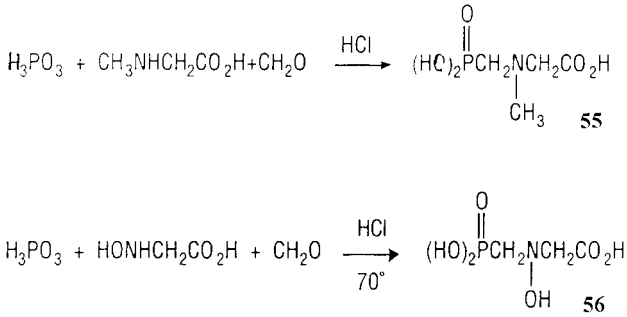


SCHEME 20

compounds contain a tertiary nitrogen and show no or only weak herbicidal activity. Furthermore, treatment of sarcosine with CH_2O and H_3PO_2/HCl produces an herbicidally inactive compound **55** (Scheme 21)

On the other hand, Franz showed [14] that N-hydroxyglyphosate **56** is an active herbicide, but less active than Glyphosate (Scheme 21). Are other substituents allowed on nitrogen that retain the herbicidal activity? To answer this question, we attempted to prepare N-amino- and azaglyphosate.



SCHEME 21

Aminoglyphosate

Several methods for the preparation of aminoalkylphosphonic and-phosphinic acids are based on the addition of a P–H bond to the C=N double bond of Schiff bases. We found that alkoxycarbonyl-hydrazinomethylphosphonates and phosphinates are formed similarly through the addition of phosphites or phosphonites to methylenecarbazate. Methylenecabazate **57** is readily formed by the reaction of benzylcarbazate with paraformaldehyde in methanol in the presence of Et_3N. The compound is obtained as a monomer of m.p. 87–91°C. On warming above 50°C for longer periods, it is converted into the trimeric hexahydrotriazine **58** of m.p. 125–127°C [15] (Scheme 22).

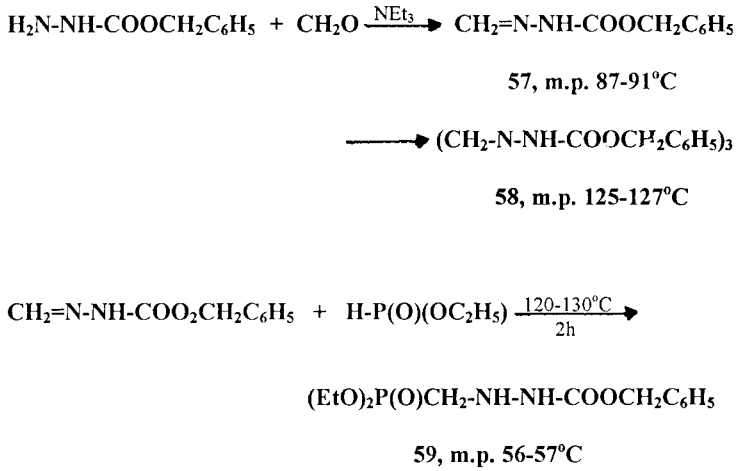
The monomeric **57** and the trimeric **58** react equally well with sec. phosphites when heated for 2 hours at 120–130°C and produce hydrazino-*N*-benzyloxycarbonyl-*N*-methyl-*O*,*O*-diethylphosphonate **59** in 88% yield [15] (Scheme 22).

Reaction of **59a** with a bromoacetate in the presence of *i*-Pr_2NEt (NaH as a base is less chemoselective and forms **60a** and **64**) as a base and a catalytic amount of 4-piperidinopyridine and KI in THF/hexane at reflux temperature yields hydrazino-*N*-benzyloxycarbonyl-*N*′-carbethoxylmethyl-N′-methyl-*O*, *O*-diethylphosphonate **60a** in 60% yield [16] (Scheme 23). The phosphinate **60b** is similarly obtained.

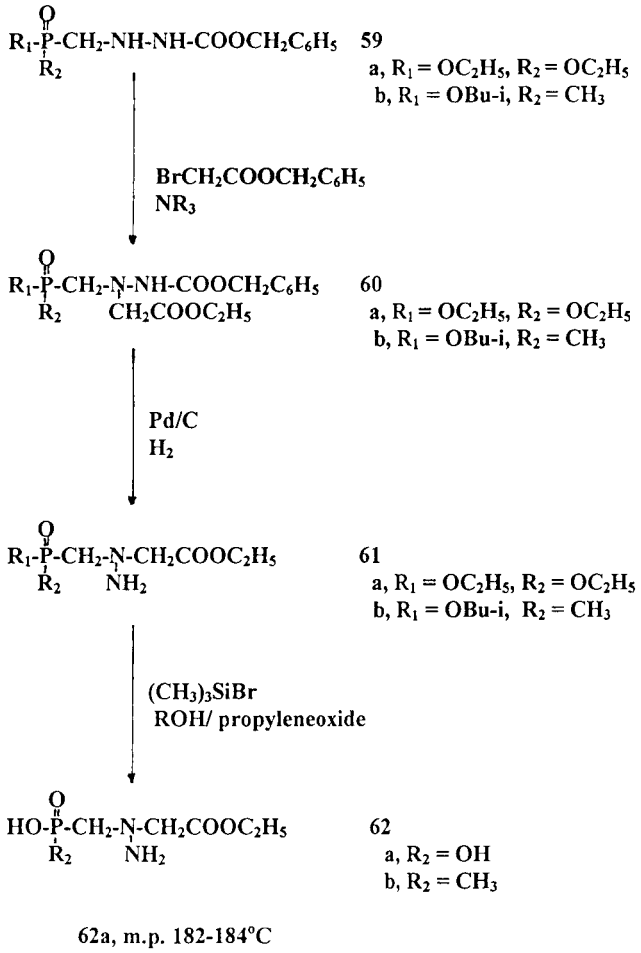
Debenzylation of **60a** to **61a** proceeds readily in ethanolic solution with H_2 in the presence of Pd/C as catalyst. Finally, dealkylation of **61a** and **61b** is achieved through the silyl esters followed by hydrolysis in ethanol/propylene oxide. The yields of the free acids **62a** and **62b** are high (Scheme 23).

HAzaglyphosate

To obtain azaglyphosate, the *N*-methylenebenzylcarbazate **57** is first reacted in THF with ethyl bromoacetate in the presence of NaH as a base to give **63**



SCHEME 22



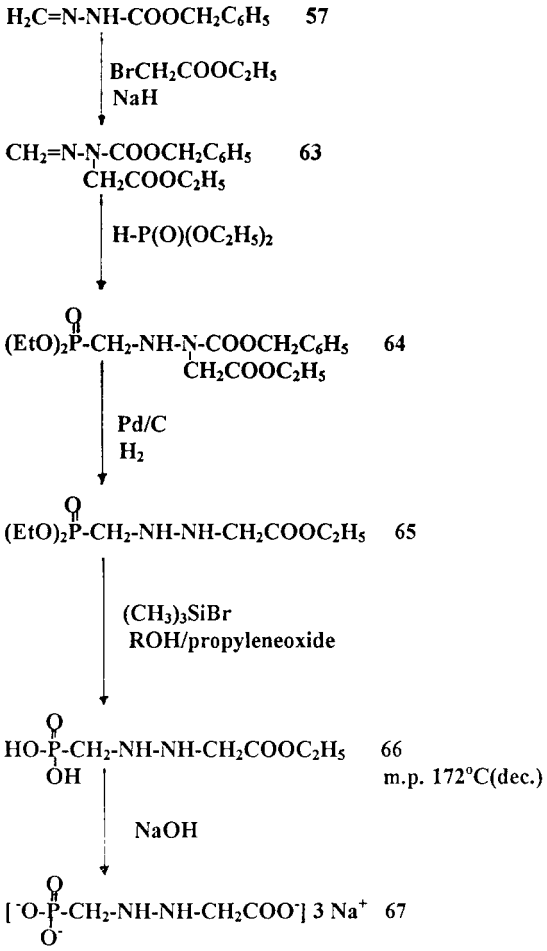
SCHEME 23

in 93% yield [16] (Scheme 24). To this intermediate is then added at 120–130°C diethyl phosphite to give the hydrazinomethylphosphonate **64** in 67% yield. Debenzylation of **64** with H_2 in the presence of Pd/C proceeds readily in ethanolic solution and yields **65** in 92% yield. Treatment of **65** with Me_3SiBr and hydrolysis of the silyl ester with ethanol/propylene oxide produces crystalline **66** of m.p. 172°C in 82% yield.

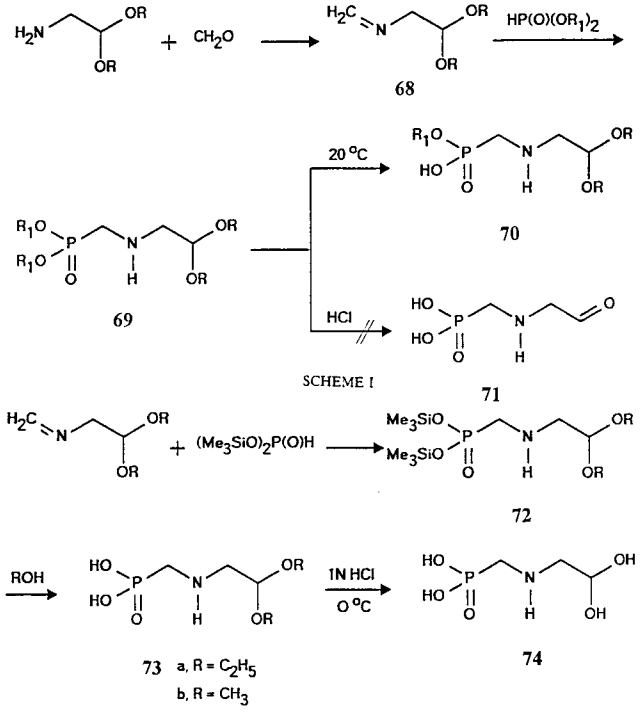
Treatment of **66** with three equivalents of NaOH yields the trisodium salt **67** (Scheme 24). The *N*-aminoglyphosate **62a** as well as the azaglyphosate **66** show PGR properties at 4 kg/ha against monocotyledonous as well as against dicotyledonous weeds. Finally, what are the requirements for the carboxylic acid part (section 5)? In the original patent by Franz [17], the free acid **1** and salts thereof, as well as esters, nitrile amides, hydrazides, and thioesters are claimed as herbicides. Of these only the acid, salts, the lower alkyl esters and the nitrile show herbicidal activity, which is, however, not as high as that of Glyphosate.

Similarly, the aldehyde of Glyphosate also showed no herbicidal activity [18]. How was the aldehyde synthesized? Reaction of methylene-aminoacetaldehyde dimethylacetal **68** with dimethyl phosphite produces the phosphonomethyl-substituted aminoactealdehyde acetal **69**. This compound, on standing at 20°C for extended periods of time, precipitated the crystalline halfester **70** [18] (Scheme 25). Attempts to hydrolyze **69** completely with HCl to give the free aldehyde **71** failed. Destruction of the molecule occurred, and a black tar was formed.

Therefore, the addition reaction of bis(trimethylsilyl) phosphite to methylene-aminoacetaldehyde



SCHEME 24



SCHEME 25

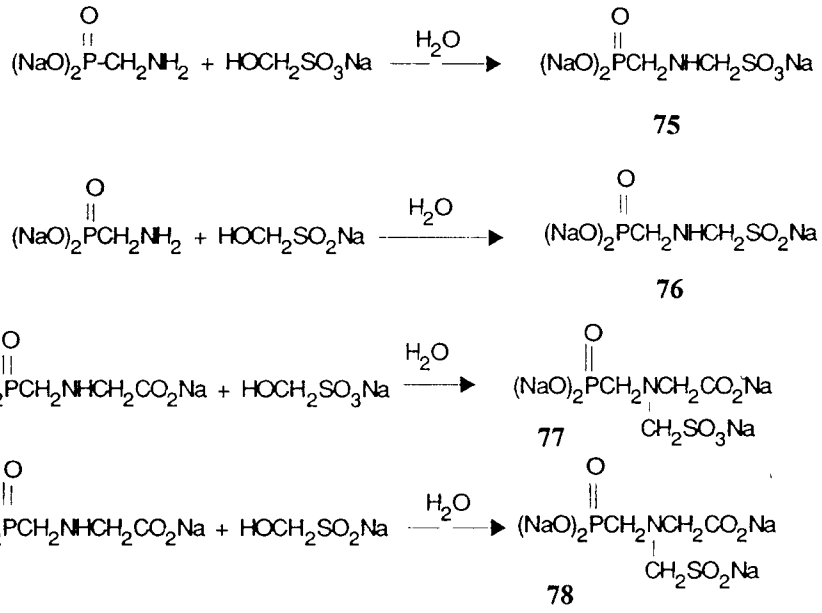
acetals was used to prepare the silyl esters **72**, which could readily be hydrolyzed by alcohol/water to the corresponding acids **73a** and **73b**. Treatment of **73b** with HCl, first at 0°C, then at 15°C, and evaporation of the reaction solution in a high vacuum at 40°C gave the *N*-phophonomethyl-aminoacetaldehyde as a brown resin which has the hydrate structure **74** [18] (Scheme 25). Furthermore, the synthesis of Glyphosate analogs, which bear, in place of the carboxylic acid group, a sulfonic **75** or sulfinic acid **76** group, was readily achieved by condensing aminomethylphosphonic acid with hydroxymethylsulfonic or -sulfinic acid under alkaline conditions at around pH 11 [19] (Scheme 26).

Furthermore, Glyphosate also reacted with hydroxymethylsulfonic and -sulfinic acid at the NH group to give the acids **77** and **78**. The compounds showed no herbicidal activity. We have made attempts to prepare bioisosteric analogs of Glyphosate such as the oxadiazoles **79** and **80**. The oxadiazole analogs **79** and **80** [20] are readily formed from chloromethyloxadiazole and aminomethylphosphonate in the presence of a base (Scheme 27).

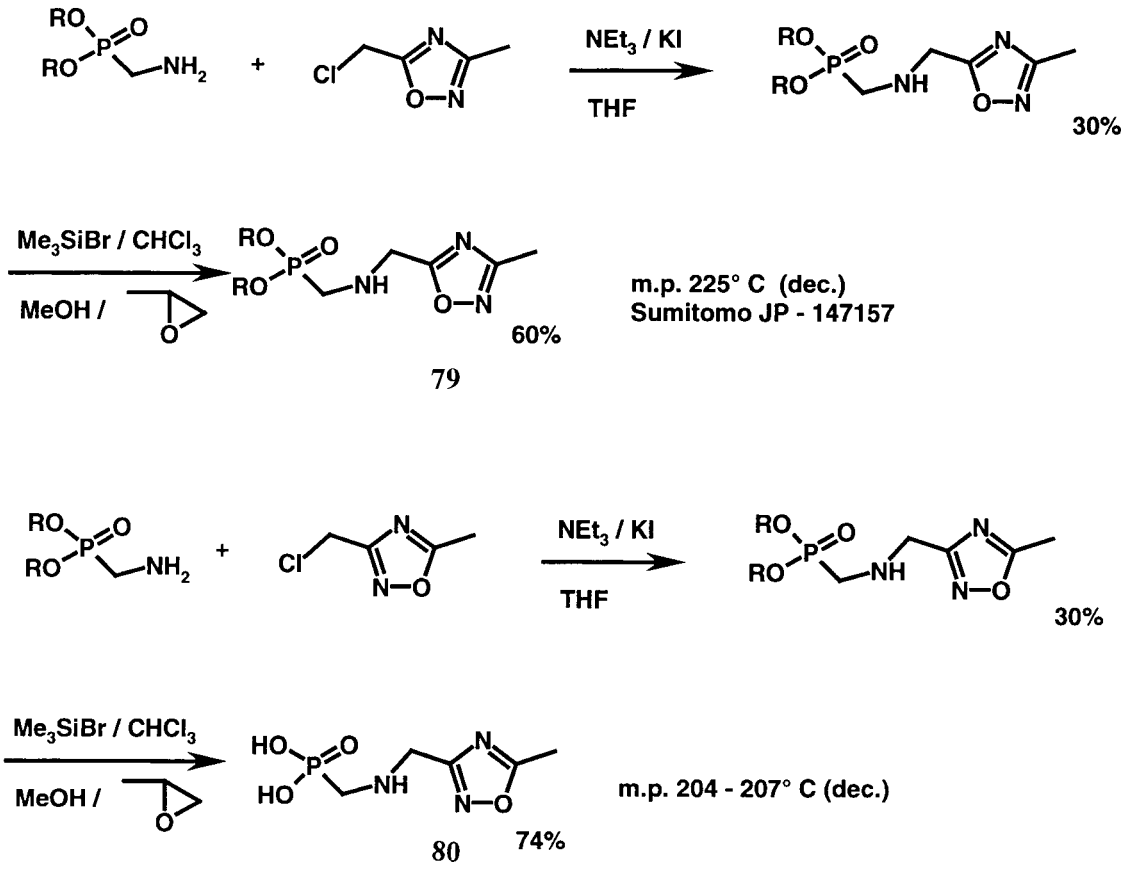
In contrast to a literature report, we were able to obtain the tetrazolylmethylamino-methyl phosphonic acid **80a** by treatment of the acylated Glyphosate nitrile with $NaN_3/BF_3.Et_2O$ in DMF [20]. The acid was also obtained when trialkyltin azide in THF, instead of NaN_3, was used [21] (Scheme 28).

Compounds **79, 80**, and **80a** showed only weak herbicidal activity. Since all our attempts to prepare a more active Glyphosate were not successful, we turned our efforts toward the synthesis of prodrugs. These are compounds that can decompose to give Glyphosate, but, because of different physical properties, may show better penetration and translocation properties. As an example, I shall report on the synthesis and properties of *N*-malonatoaminomethphosphonic acid [22]. Heating of *N*-benzylaminomethylphophonate with a suitable bromomalonate in alcoholic solution at reflux produces the phophonates **81** in high yield. Debenzylation with H_2/Pd/C proceeds with high yield to give **82**. Treatment of **82** with Me_3SiBr followed by ROH/H_2O yields the free phosphonic acid **83** (Scheme 29). On the other hand, heating of **82** with NaOH produces **84**, which still contains one ester group on phosphorus.

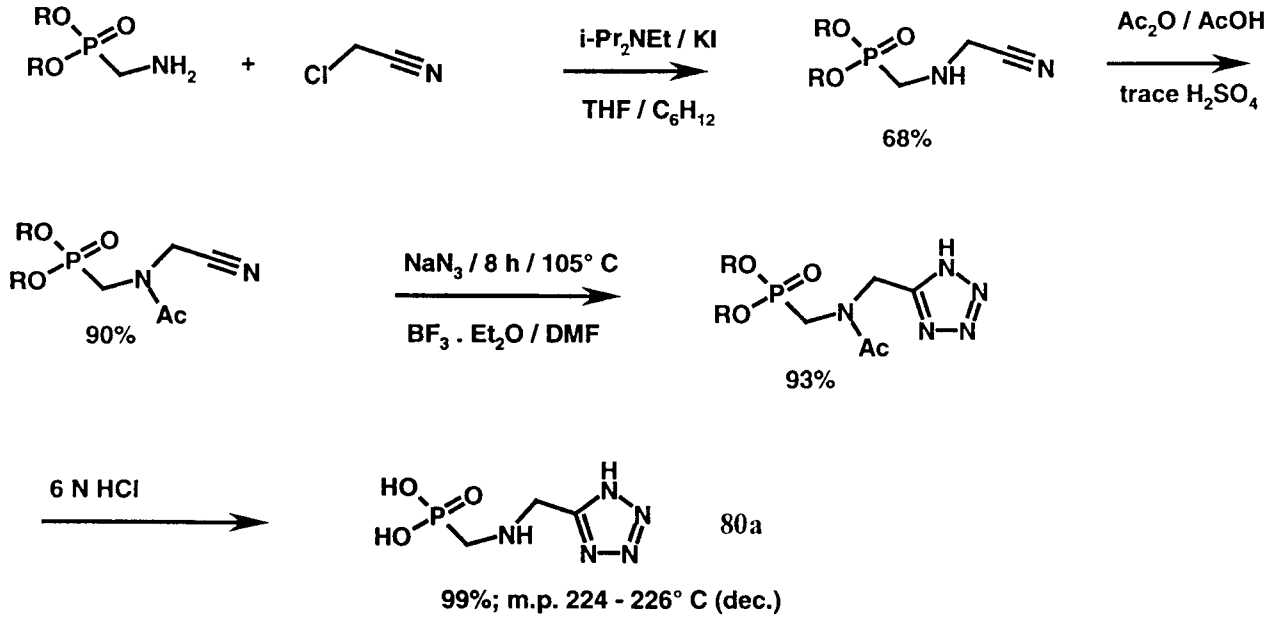
To obtain the tetrasodium salt **88**, the compound



SCHEME 26



SCHEME 27



SCHEME 28

TABLE 1 Dependence of the Postemergent Herbicidal Activity of **86a**, **86b**, and Glyphosate from the Concentration against Five Monocotyledonous and Seven Dicotyledonous Weeds

		% Activity		
	Concentration	*86a*[a]	86b[b]	Glyphosate[c]
Formulated	2 kg/ha	73	86.5	90.6
	1 kg/ha	42.7	76	71.9
	0.5 kg/ha	23	46.9	27.1
Not formulated, only dissolved in water	2 kg/ha	37.5	69.8	82.3
	1 kg/ha	25.0	55.2	74.0
	0.5 kg/ha	3.1	17.7	36.5

[a] $H_2O_3PCH_2NH\text{-}CH(CO_2Et)_2$.
[b] $H_2O_3PCH_2NH\text{-}CH(CO_2CH_3)_2$.
[c] $H_2O_3PCH_2NHCH_2CO_2H$.

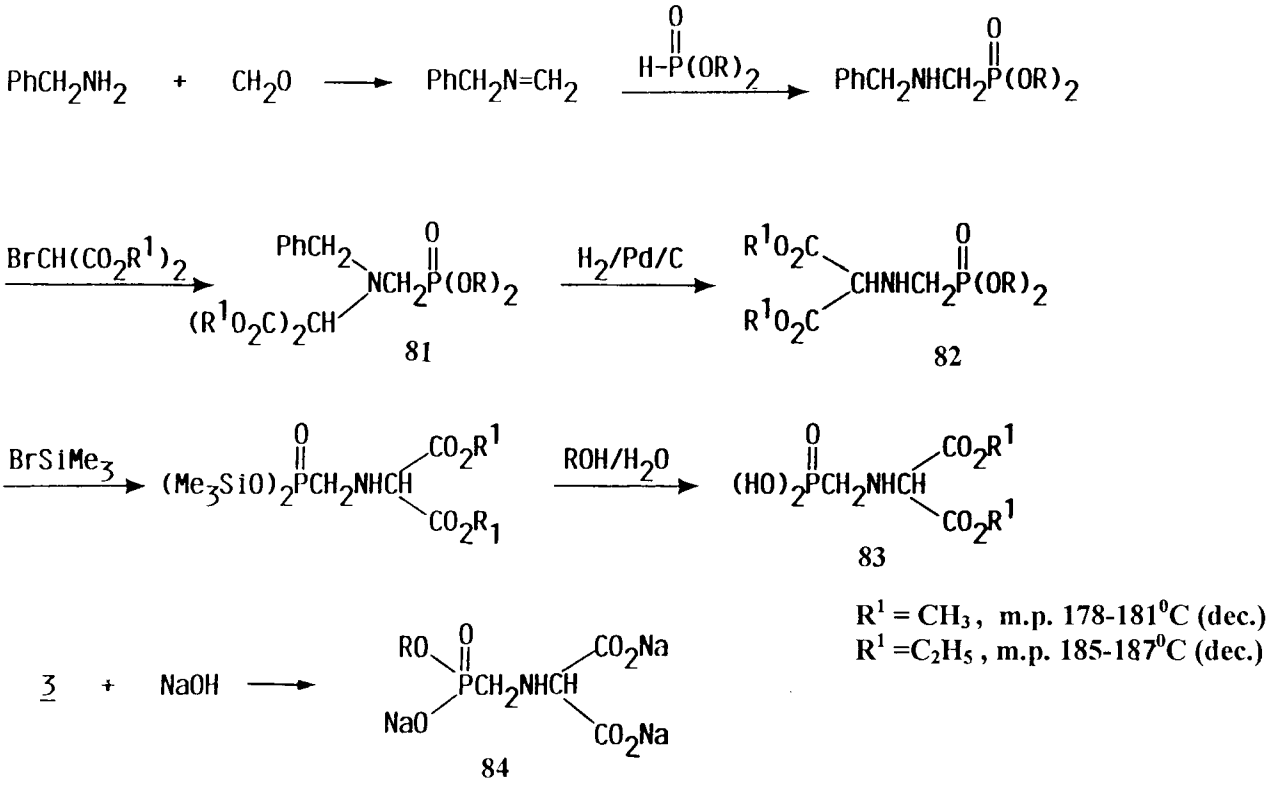
86 is treated with four equivalents of NaOH. From this salt, the free tetra-acid **89** can be liberated by ion exchange. It was characterized as the di-isopropylamine salt **90** (Scheme 30). Concentration of the aqueous solution of the free acid at 0–10°C in a vacuum liberated CO_2 and gave a solid which consisted of a 1:1 mixture of the tetra-acid **89** and Glyphosate **1**.

On letting this mixture stand at room temperature, CO_2 was evolved, and, after 3 weeks, the tetra-acid had disappeared and only Glyphosate was present (Scheme 30). Acidic hydrolysis of **82** produced quantitatively Glyphosate. The same procedure may be used for the preparation of the phosphinic acid analogs [22]. The dependence of the postemergent herbicidal activity of **86a, 86b**, and Glyphosate from the concentration against five monocotyledonous and seven dicotyledonous weeds is shown in Table 1. The formulated compounds in the first row were used (*i*-$PrNH_2$, tenside, and H_2O), and the compounds in the second row were only dissolved in water [22]. As indicated by the data, when formulated, the dimethyl ester **86b** has about the same herbicidal activity as Glyphosate, whereas the diethyl ester **86a** is a bit weaker. When only dissolved in H_2O, Glyphosate is more active by a factor of 2 to 4 than **86a** and **86b**. This difference stems from the fact that the *i*-$PrNH_2$ salts of **86a** and **86b** are not stable in H_2O but hydrolyze, decarboxylate, and give first the Glyphosate ester than Glyphosate. Thus, pure Glyphosate could be isolated from a formulated solution of **86a** [22].

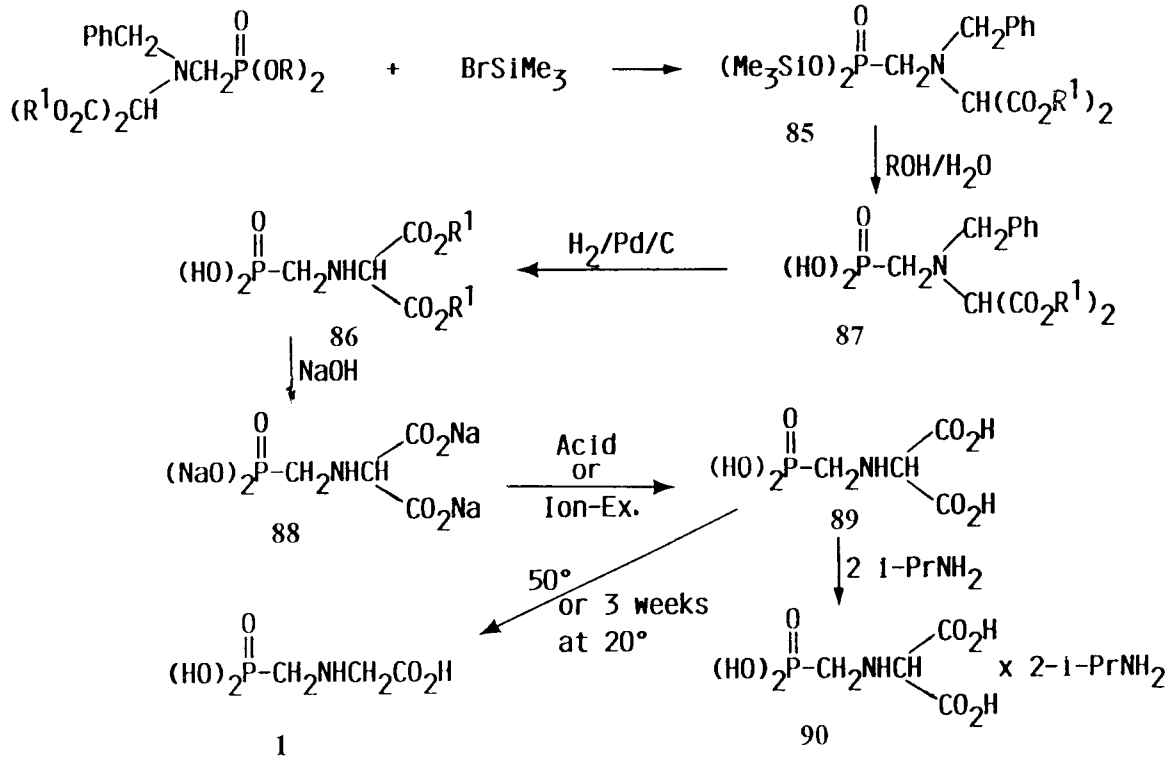
Even the pure diesters **86a** and **86b** dissolved in D_2O are not stable indefinitely. Quantitative ^{13}C and ^{1}H NMR measurements for **86a** gave a half live of $t_{1/2}$ = 60 days and for **86b** $t_{1/2}$ = 8.5 + 0.5 days. The salts decompose also. Thus, for aqueous solutions of the Na-, Me_2NH_2-, and i-$PrNH_3$ salt of **86a**, a half life of about 10 days was observed at 20°C. The tetrasodium salt **88**, however, is stable in the solid state as well as in solution. It shows PGR properties but only weak herbicidal activity.

CONCLUSIONS

To conclude this review, I want to stress the fact that there is no other compound presently known that



SCHEME 29



SCHEME 30

has the same high herbicidal activity as Glyphosate. Why is Glyphosate so unique? As shown by Amrhein and his coworkers [23], it inhibits the enzyme 5-enolpyruvylshikimic acid-3-phosphate synthetase (EPSP), which leads to an accumulation of shikimic acid and a deficiency in aromatic amino acids and phenolic compounds. Since this pathway is only observed by plants, it is nontoxic or only of low toxicity to all animals. Furthermore, Glyphosate is readily metabolized by soil microbes. Our present knowledge was recently summarized in two monographs [1,24]. Thus, when applied to soil, Glyphosate was metabolized within 24 hours to give aminomethylphosphonic acid (3%), CO_2, NH_3, and H_3PO_4. In the plant, breakdown is much slower and the following metabolites have been detected: CO_2, aminomethylphosphonic acid, and glyoxalate.

Of 78 important weeds, 76 are controlled by Glyphosate. Only Equiseturn and fern are not attacked by Glyphosate. It has recently been suggested that these two weeds have an overproduction of the enzyme 5-enolpyruvylshikimic acid-3-phosphate and thus withstand Glyphosate. It has also been reported that these two weeds metabolize Glyphosate [1].

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