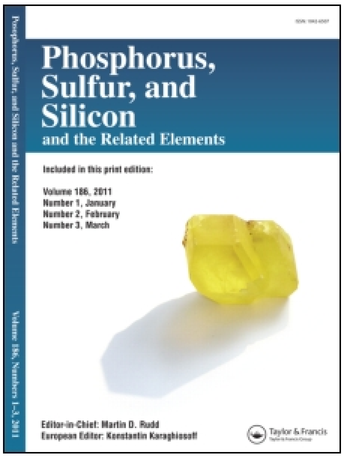

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Hall, Roger G.(2008) 'The Role of Phosphorus in Crop Protection: Commercial and Experimental Weed Control Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 2, 258 — 265
To link to this Article: DOI: 10.1080/10426500701734216
URL: http://dx.doi.org/10.1080/10426500701734216

Phosphorus, Sulfur, and Silicon, 183:258–265, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701734216

The Role of Phosphorus in Crop Protection: Commercial and Experimental Weed Control Agents

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During the last ten years there have been significant changes in the role that Phosphorus has played in Crop Protection. In commercial terms, sales of organophosphate insecticides have steadily declined; this has been due to the withdrawal of a number of products due to regulatory and industry pressure, along with the introduction of safer, lower-use rate insecticides. With herbicides, the story is different; due to the introduction of genetically modified crops, sales of products such as Glyphosate and Glufosinate have increased. In the area of fungicides, Phosphorus has so far had little impact. Despite these successes, new crop protection agents containing Phosphorus that have reached the market place remain elusive. In this article, I discuss some recent market trends and summarize some approaches toward identifying new herbicides containing Phosphorus.

Keywords Bio-isosteres; herbicidal activity; phosphonic acids; transition State Analogs

COMMERCIAL ASPECTS

Phosphorus has had a significant impact on Crop Protection, with many important products reaching the market place. The two most important classes of products are insecticides and herbicides, which are summarized in this section.

Organophosphate Insecticides

The Organophosphate class of insecticides began with the introduction of parathion in the 1940s and included more than 100 products displaying a broad range of activity and physical chemical properties. A number of these products are, however, highly acutely toxic and have been withdrawn from the market. An excellent overview[1] has been presented at this meeting and further details can be found in the full paper.

The author would like to acknowledge Keith Baylis, John Weetman, Ichiro Mori, Fred Cederbaum, Hans-Peter Buser, and John Dingwall (deceased).
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Phosphorus-Containing Amino Acid Herbicides

Three compounds belong to this class; Glyphosate was introduced to the market in 1972. Bialafos is a natural product obtained by fermentation; introduced in 1984, this tripeptide has remained a relatively small product in terms of sales. Glufosinate is the amino acid of Bialafos and was marketed in 1986. Sales for this class of herbicide have risen by 4.8% per year over the last five years;[2] this is remarkable in a market that has seen little or no growth and can be explained by the introduction of genetically modified crops. In the United States, increasing acreages of crops engineered to be resistant to treatments of Glyphosate or Glufosinate are being planted, and include soy beans, cotton, and maize. Additionally, crops engineered to be both resistant to herbicides and insect damage should ensure the steady use of such herbicides, although certain weeds are now becoming resistant to Glyphosate treatments.

EXPERIMENTAL WEED CONTROL AGENTS

A number of approaches are available to search for and identify biologically active compounds. These include random screening, testing natural products, targeted synthesis of molecules from literature sources (patent examples of chemical literature) and rational design. I shall discuss some efforts that use the last approach.

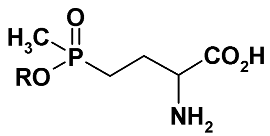
Rational Design of Phosphorus-Containing Bioactives

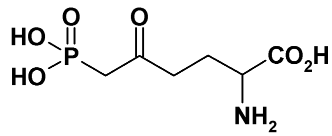
Three main opportunities exist for the rational design of Phosphorus-containing Bioactives: 1. Transition State Analogs, where the tetrahedral phosphorus mimics the transition state of, for example, an amide bond formation or cleavage. This approach has been successful in the pharmaceutical area;[3] 2. bio-isosteric replacements of carboxylic acids by phosphorus; this approach was successful again in the pharmaceutical area where new GABA-B antagonists were discovered;[4] and 3. stable mimics of phosphorylated substrates; here many mimics of biologically important phosphates have been prepared, but a commercial product based on this approach has not yet resulted. Phosphonic acids remain, however important compounds; due to their di-valent character they exhibit important properties such as metal chelation[5] or strong binding to arginine residues in proteins.

In the search for new weed control agents, I shall discuss our efforts using the three approaches listed above.

Transition-State Analogs

Plants incorporate nitrogen using the enzyme Glutamine Synthetase (GS), which converts Glutamic Acid to Glutamine. Glufosinate (**1**) acts by inhibiting this enzyme; it is itself phosphorylated and closely mimics the transition state.[6] A beta-keto phosphonate (**2**) was reported[7] to also inhibit GS, and we started a program to identify herbicides with improved activity.

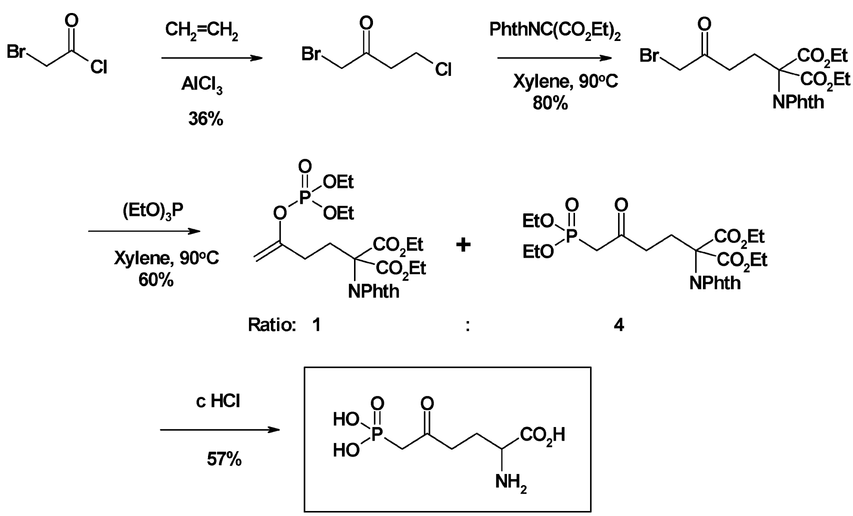




R = H Glufosinate (1) (2)

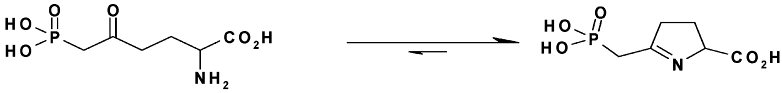
R = $P(O)_3^-$ Phosphorylated (1)

CD could not be reproduced and the route shown in scheme 1 was developed. The reported synthesis of (**2**). The Arbusov reaction led to a mixture of the required ketone and the Perkow product, easily separated by chromatography.



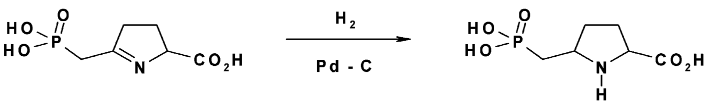
SCHEME 1

We found that compound (**2**) exists in the cyclic pyrroline form (**3**). There is a pH dependence, but even at low pH only ca. 30% exists in the open chain form (**2**), as seen by ^{31}P and ^{13}C n.m.r. Further evidence was provided by the catalytic reduction to the pyrrol (**4**), Scheme 2.



(2) (3)

pH		
> 7	0	100
0.25	1	3



(4)

SCHEME 2

Unfortunately the pyrroline (**3**) and other analogs proved to be weaker inhibitors of GS than Glufosinate, and less active as herbicides in whole plant assays.

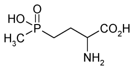
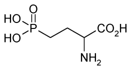
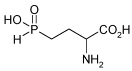
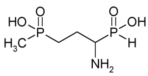
Bio-isosteric Replacements of Carboxylic Acids

We have previously reported[8,9] the synthesis of α-aminophosphinic acids R-PO_2H_2 as analogs of the protein amino acids. Although the P—O and P—C bonds are 15–20% longer than the C—O and C—C bonds in the carboxylate group, the overlap of the key binding atoms is good. Using X-ray data it appears that the Phosphorus atom sits above the plane of the carboxyl group, giving good overlap of the two oxygen atoms; when the additional ligand on the Phosphorus is the smallest, hydrogen, there appears to be enough room at various receptors or protein surfaces for good binding.

This is supported by the fact that of 20 analogues of the protein amino acids, 9 have shown interesting biological activity ranging from nematicidal, antibiotic, plant growth regulation and fungicidal. In contrast, from over 50 analogs prepared of non-natural amino acids, only 1 showed weak biological activity.

Turning back to Glufosinate, Table I nicely illustrates this concept. Replacing the methyl phosphinic moiety by other Phosphorus acids leads to a dramatic fall-off in activity; however, the replacement of the carboxylic acid by PO_2H_2 gives a compound which retains most of the

TABLE I Herbicidal Activity on Weeds (4 kg/Ha)

Structure	Avena	Setaria	Lolium	Solanum	Sinapsis	Phaseol
	1	1	2	1	1	1
	9	7	9	5	6	8
	5	6	6	5	2	8
	3	1	3	2	2	2

1 = Good Activity; 9 = No Activity.

activity. However, the same approach in a series of Glyphosate analogues leads to a dramatic loss of activity, as shown in Table 2.

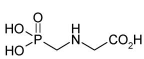
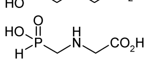
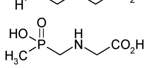
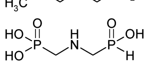
Stable Mimics of Phosphorylated Substrates

Imidazole Glycerol Phosphate Dehydratase (IGPD) is an enzyme involved in the biosynthesis of Histidine the inhibition of which has been reported[10] to exhibit herbicidal effects in plants. Two approaches have been employed to identify novel IGPD inhibitors, as shown in Scheme 3.

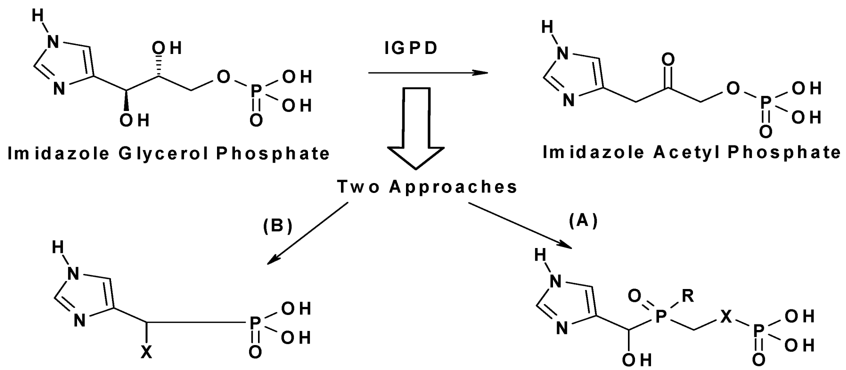
In the first approach (A), the synthesis of phosphinates and phosphine oxides is shown in Scheme 4. Unfortunately all compounds were inactive as herbicides.

In a second approach (B), simplified Phosphonic acids were prepared that proved to be potent inhibitors of IGPD, Scheme 5. Triazoles, either C- or N- bound proved to be more potent than imidazoles.

TABLE II Herbicidal Activity on Weeds (4 kg/Ha). 1 = Good activity; 9 = no activity

Structure	Avena	Setaria	Lolium	Solanum	Sinapsis	Phaseol
	2	1	2	1	2	2
	8	8	7	6	7	8
	5	3	4	5	5	3
	7	9	9	9	7	9

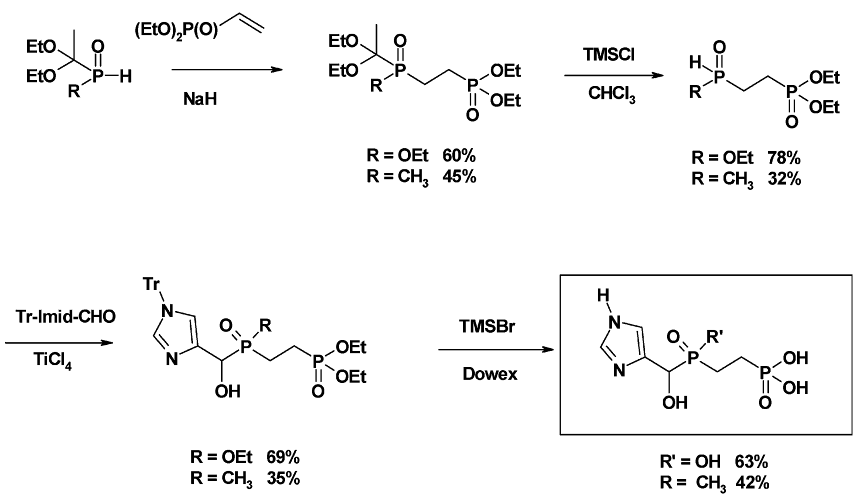
1 = Good activity; 9 = no activity.



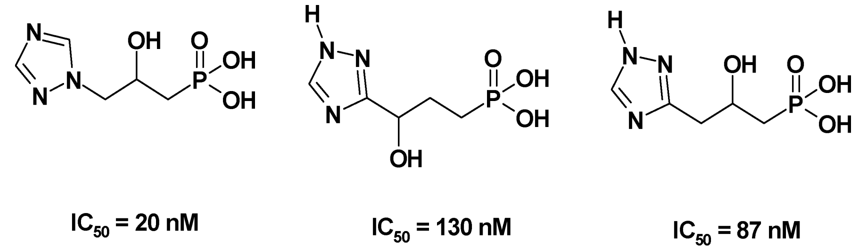
SCHEME 3

Further improvements to in vitro activity were achieved by restricting the conformational freedom of such compounds; the cyclohexane derivative is a good example.[11] (**5**) exhibiting an IC_{50} of 40 nM. Chirality was also an important aspect, where the two enantiomers were separated using a chiral column, Scheme 6.

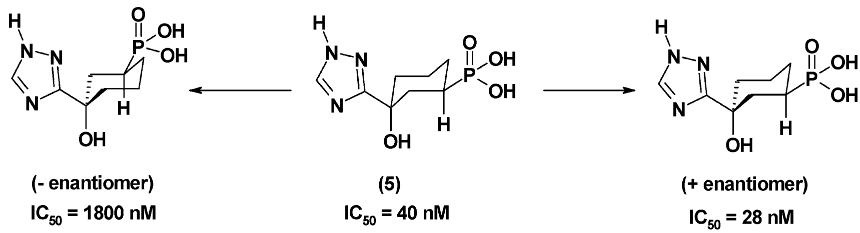
Despite the potency of such compounds observed at the enzyme level, high levels of activity in whole plant assays were not observed. In addition, any herbicidal effects were seen after a period of time. Interestingly when such compounds were injected into plants, high potentcy



SCHEME 4



SCHEME 5

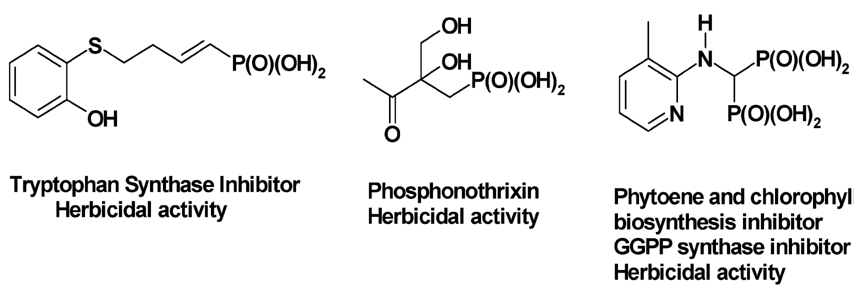


SCHEME 6

and a rapid onset of action were observed, suggesting that plant uptake and/or translocation of these phosphonic acids are poor.

OUTLOOK AND CONCLUSIONS

Other structures have appeared recently which contain Phosphorus and display herbicidal activity, Scheme 7. These may offer further opportunities for optimisation programs in the search for new commercial products.



SCHEME 7

It does seem that in Crop Protection, phosphorus-containing compounds show a propensity towards exhibiting herbicidal activity; the generally poor activity observed in whole plant assays begs the question as to whether pro-forms of phosphonic acids should be more systematically investigated. However, it must be said that with our current knowledge, the rational design of phosphorus-containing Weed Control Agents has not yet been successful.

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