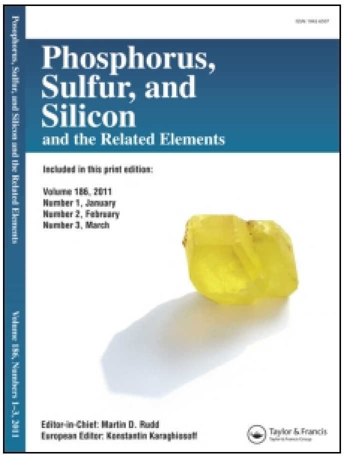

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New carboxyphosphonic and phosphinic acid structures of technical and biological interest

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NEW CARBOXYPHOSPHONIC AND PHOSPHINIC ACID STRUCTURES OF TECHNICAL AND BIOLOGICAL INTEREST

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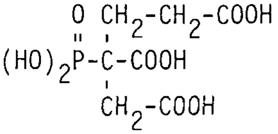
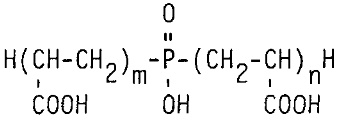
Carboxyphosphonic and phosphinic acids have recently found applications in the diverse fields of industrial water treatment and pesticides. For example, the acids 1 and 2 are ferrous corrosion inhibitors and scale control agents for circulating industrial water systems, the amino acid 3 is a translocateable total herbicide and the naturally occurring glutamic acid analogue 4 has antibacterial, fungicidal and herbicidal properties. This paper presents a selection of our results on the synthesis of new carboxyphosphonic and phosphinic acids which led to corrosion and scale control agents and structures related to natural products, and their postulated biogenetic precursors.



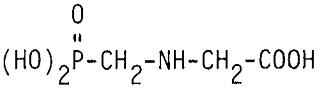
$(HO)_2\overset{O}{\overset{\|}{P}}-\underset{CH_2-COOH}{\overset{CH_2-CH_2-COOH}{C}}-COOH$

(1)



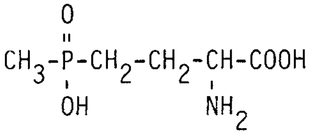
$H(\underset{COOH}{CH}-CH_2)_m-\underset{OH}{\overset{O}{\overset{\|}{P}}}-(CH_2-\underset{COOH}{CH})_nH$

(2)



$(HO)_2\overset{O}{\overset{\|}{P}}-CH_2-NH-CH_2-COOH$

(3)

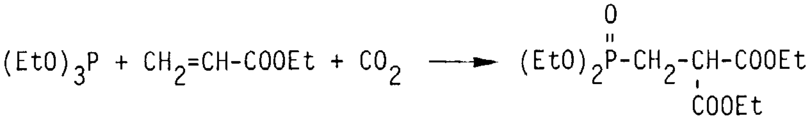


$CH_3-\underset{OH}{\overset{O}{\overset{\|}{P}}}-CH_2-CH_2-\underset{NH_2}{CH}-COOH$

(4)

Synthesis of substituted carboxyphosphonic acid corrosion and scale control agents

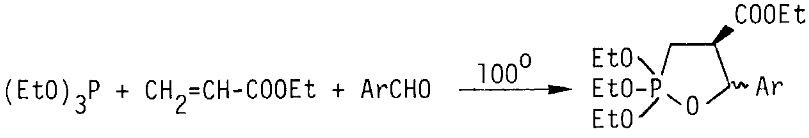
As part of an investigation of structure-activity relationships of corrosion inhibitors we needed a number of 2-substituted phosphonopropionic acids. A central intermediate for their preparation was the phosphonomethyl malonate 5, prepared either by the one-pot reaction of diethylmalonate, triethylphosphite and paraformaldehyde[1] or by the trapping of the zwitterion formed from triethylphosphite and ethylacrylate with carbon dioxide and concomitant alkylation of the carboxylate anion.



$$(EtO)_3P + CH_2{=}CH\text{-}COOEt + CO_2 \longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}\text{-}CH_2\text{-}\underset{\underset{COOEt}{|}}{CH}\text{-}COOEt$$

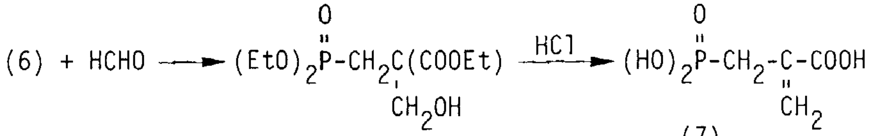
(5)

Replacement of the carbon dioxide with an aromatic aldehyde led to a simple one-pot synthesis of the pentacovalent oxaphospholans 6 as 1 : 1 cis/trans mixtures.



(6)

Alkylation of the malonate 5 followed by hydrolysis and decarboxylation gave a range of 2-substituted phosphonopropionic acids. Hydroxymethylation followed by strong acid hydrolysis gave a convenient one-pot synthesis of 2-phosphonomethylacrylic acid (7), an itaconic acid analogue and biologically interesting as an isostere of phosphoenolpyruvate[2]. Reaction of the acid 7 or its esters with nucleophiles (carbon, oxygen, nitrogen, sulphur and phosphorus) gave a further range of 2-substituted phosphonopropionic acids.



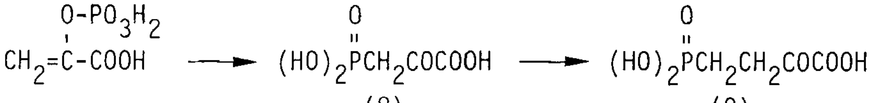
$$(6) + HCHO \longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}\text{-}CH_2\underset{\underset{CH_2OH}{|}}{C}(COOEt) \xrightarrow{HCl} (HO)_2\overset{\overset{O}{\|}}{P}\text{-}CH_2\text{-}\underset{\underset{CH_2}{\|}}{C}\text{-}COOH$$

(7)

In an approach to sterically congested carboxyphosphonic acids we examined the oxidation of readily accessible γ-ketophosphonates. Nitric acid oxidation of the acids provided an inexpensive route to carboxyphosphonic acids with outstanding properties as corrosion and scale control agents[3].

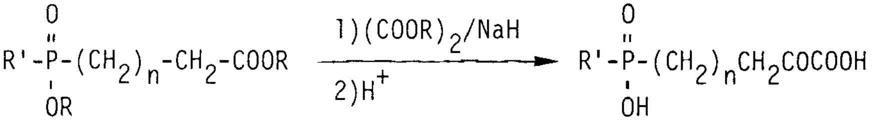
Carboxyphosphonic and phosphinic acids in the synthesis of natural products, their analogues and biogenetic precursors

In the past 12 years an increasing number of biologically active phosphorus containing amino acids have been isolated from natural sources. Biosynthetic schemes have been postulated[4] for these β- and γ-amino phosphorus acids, the key carbon-phosphorus bond forming step being a rearrangement of phosphoenolpyruvate to the ketosuccinate analogue 8, followed by homologation via the tricarboxylic acid cycle to the ketoglutarate analogue 9. The α-keto acids 8 and 9 are then converted via transamination to β- and γ-amino acids respectively.



$$CH_2{=}\underset{}{\overset{O\text{-}PO_3H_2}{C}}\text{-}COOH \longrightarrow \underset{(8)}{(HO)_2\overset{O}{\overset{\|}{P}}CH_2COCOOH} \longrightarrow \underset{(9)}{(HO)_2\overset{O}{\overset{\|}{P}}CH_2CH_2COCOOH}$$

We were interested in the biological activities of such ketoglutarate analogues and higher homologues and synthesised them by crossed Claisen condensations of the esters 10 with oxalates.

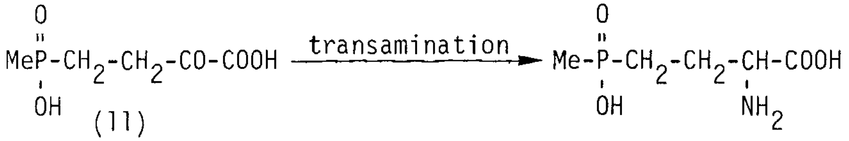


$$R'\text{-}\underset{OR}{\overset{O}{\overset{\|}{P}}}\text{-}(CH_2)_n\text{-}CH_2\text{-}COOR \xrightarrow[2)H^+]{1)(COOR)_2/NaH} R'\text{-}\underset{OH}{\overset{O}{\overset{\|}{P}}}\text{-}(CH_2)_nCH_2COCOOH$$

(10)

R' = OH, Me
n = 1, 2

Of particular interest was the biological activity of the α-keto acid 11, a potential "prodrug" of the herbicide Phosphinothrycin.

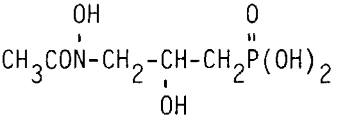


$$Me\underset{OH}{\overset{O}{\overset{\|}{P}}}\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}COOH \xrightarrow{\text{transamination}} Me\text{-}\underset{OH}{\overset{O}{\overset{\|}{P}}}\text{-}CH_2\text{-}CH_2\text{-}\underset{NH_2}{CH}\text{-}COOH$$

(11)

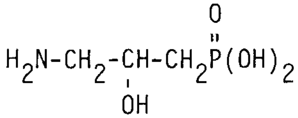
Phosphinate 11 was an active herbicide with the same characteristics as Phosphinothrycin, but unlike Phosphinothrycin did not inhibit the enzyme glutamine synthetase[5].

Fujisawa workers[4] have isolated a family of antibiotic γ-amino acids derived from Streptomyces species, including the hydroxamic acid 12.



$$CH_3CO\overset{OH}{N}\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}CH_2\overset{O}{\overset{\|}{P}}(OH)_2$$

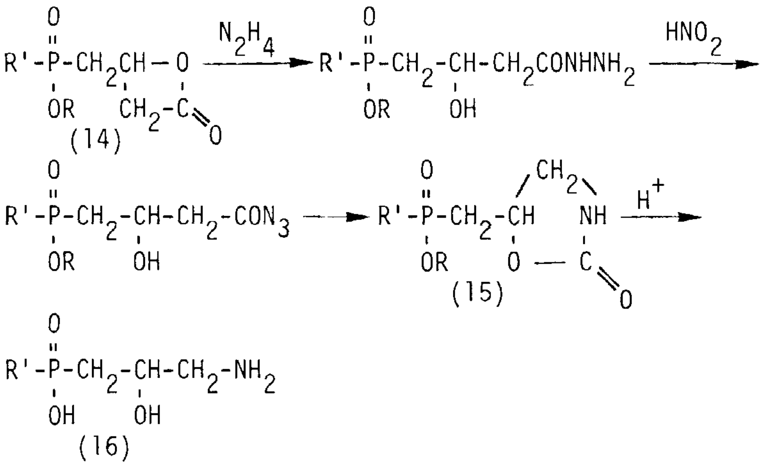
(12)



$$H_2N\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}CH_2\overset{O}{\overset{\|}{P}}(OH)_2$$

(13)

We have synthesised the parent amino acid 13 and two analogues using as intermediates the β-lactones 14, which are prepared in almost quantitative yield by free radical catalysed addition of phosphites and phosphonites to diketene[6]. Ring opening with hydrazine followed by Curtius reaction led cleanly to the oxazolidinones 15 which on acid hydrolysis gave the acids 16 in overall yields of ca. 80 % based on diketene.



R' = OH, Me, Et

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