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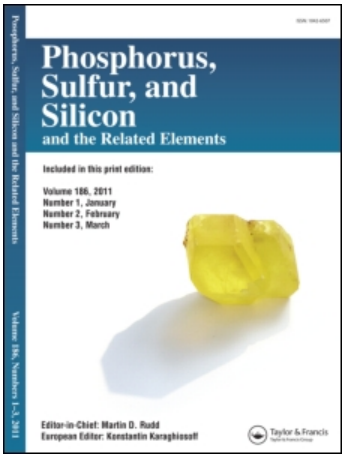

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Synthesis and properties of phosphinothricin derivatives

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SYNTHESIS AND PROPERTIES OF PHOSPHINOTHRICIN DERIVATIVES

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Abstract The synthesis and properties of phosphinothricin derivatives which have different alkyl groups attached to phosphorus or bear a substituent on the nitrogen are described and their biological activities discussed.

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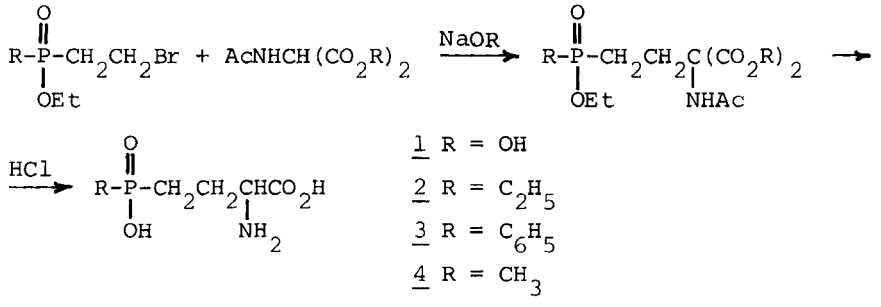
INTRODUCTION

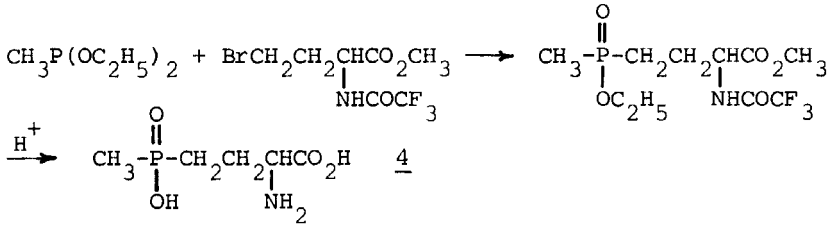
It has been known for more than twenty years[1] that the phosphonic (1) and phosphinic acid (2) analogs of glutamic acid possess inhibitory properties towards glutamine synthetase, whereas the phenyl derivative (3) has only slight inhibitory activity. The synthesis of the ethyl (2) and phenyl phosphinic acid (3) analogs of glutamic acid was accomplished by condensation of diethyl acetaminomalonate with the corresponding phosphinates, followed by hydrolysis of the crude reaction mixture[2]:



1 R = OH
2 R = C_2H_5
3 R = C_6H_5
4 R = CH_3

The phosphonic analog was synthesized in the same way[3], starting from 2-bromoethylphosphonate. Phosphinothricin (4) has been isolated from cultures of Streptomyces viridochromogenes[4] and Strepto-

myces hygroscopicus[5] as the tripeptide, phosphonothricylalanylalanine. Phosphinothricin, as the ammonium salt, is now being developed as a contact herbicide[6]. The first synthesis of phosphinothricin was reported by Zaehner et al.[4] using in the final step an Arbusov reaction of a homoserine derivative followed by hydrolysis.



More recently several other syntheses of phosphinothricin have been reported which have been reviewed by us[7].

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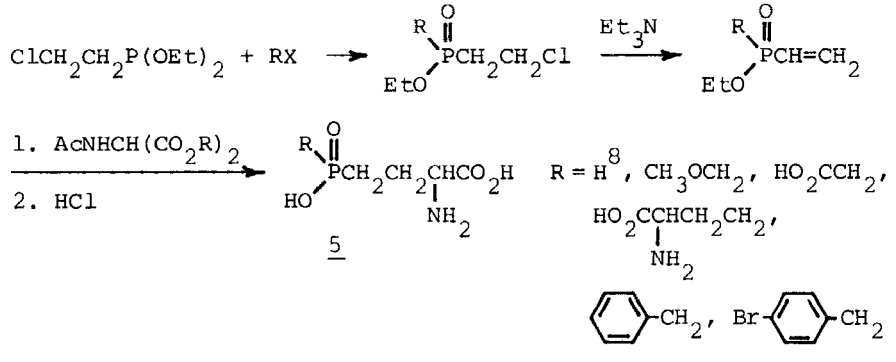
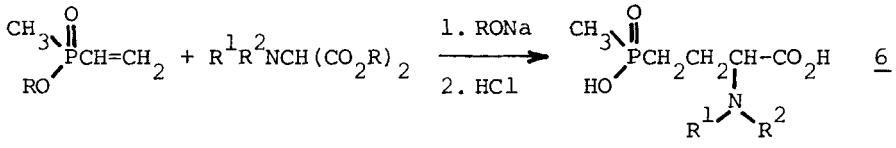
RESULTS AND DISCUSSION

We have found a general procedure for the preparation of phosphinothricin derivatives which have different alkyl groups attached to phosphorus or bear a substituent on the nitrogen. Thus we observed that diethyl-2-chloroethylphosphonite undergoes a Michaelis-Arbusov reaction with alkyl halides and yields 2-chloroethyl-substituted phosphinates which have been converted by the conventional acylaminomalonate procedure to phosphinothricin derivatives, 5.



Phosphinothricin derivatives, which bear substituents on the nitrogen 6, have been obtained by the base catalyzed addition of substi-

tuted aminomalonates to methyl-vinylphosphinates followed by hydrolysis.



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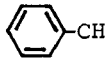
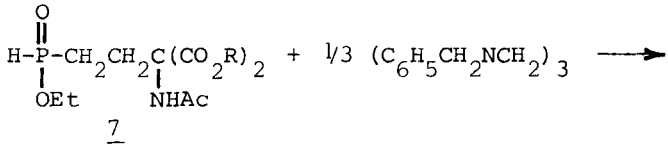
R^1 = H,  ; R^2 = CH_3,  ; R^1, R^2 = $(CH_2)_n$; n = 4-6

Like in other aminosubstituted phosphinic acid compounds[7] the ^{31}P-chemical shift of these phosphinothricin derivatives 5 and 6 is strongly dependent on the pH of the solution. It is therefore clear that all acids possess the betaine structure. The phosphonite half ester 7 shows the typical reactions of P-H containing compounds; thus it added easily to N,N',N"-tribenzylhexahydrotriazine and yielded after hydrolysis and debenzylation 3-amino-3-hydroxycarbonyl-aminomethylphosphinic acid 8 in high yield.



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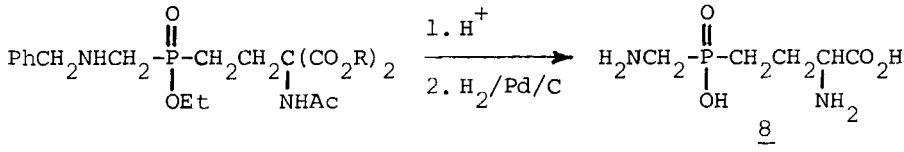

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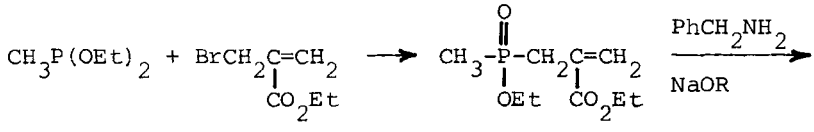
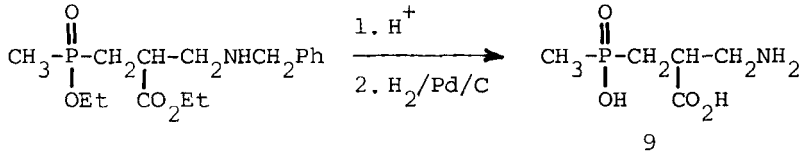
The structural isomer 9 of phosphinothricin was prepared in the following way:





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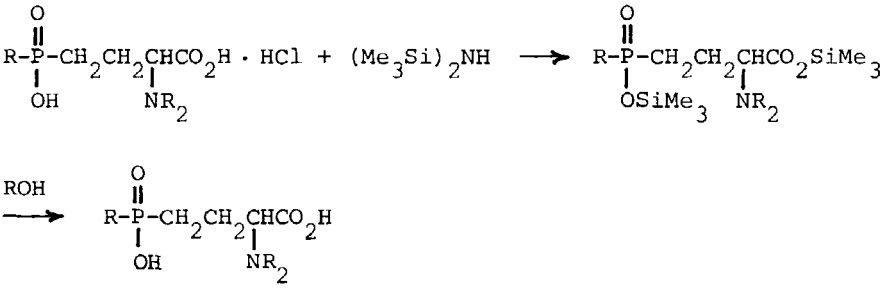
Sometimes recrystallization and other purification procedures of the phosphinothricin derivatives failed to give pure acids. It was, however, found that silylation of the crude hydrochlorides by refluxing with excess hexamethyldisilazane, then distillation, followed by hydrolysis with ethanol produced the acids in a crystalline state and an excellent purity, e.g.



This purification procedure could also be applied to the phosphonous and phosphonic acid derivatives.

BIOLOGICAL ACTIVITY

A comparison of the glutamine synthetase inhibition and the contact herbicidal activity of phosphinothricin derivatives shows that they run about parallel in those cases where the mode of action is the same.

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