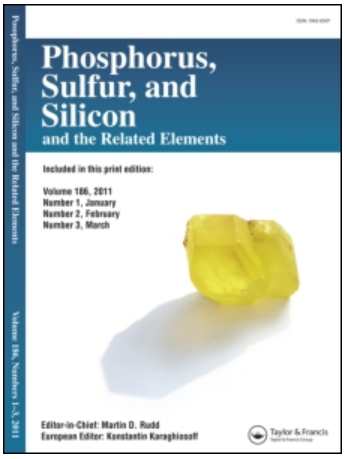

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Aminooxyalkylphosphonic Acids and Derivatives

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AMINOOXYALKYLPHOSPHONIC ACIDS AND DERIVATIVES [1]

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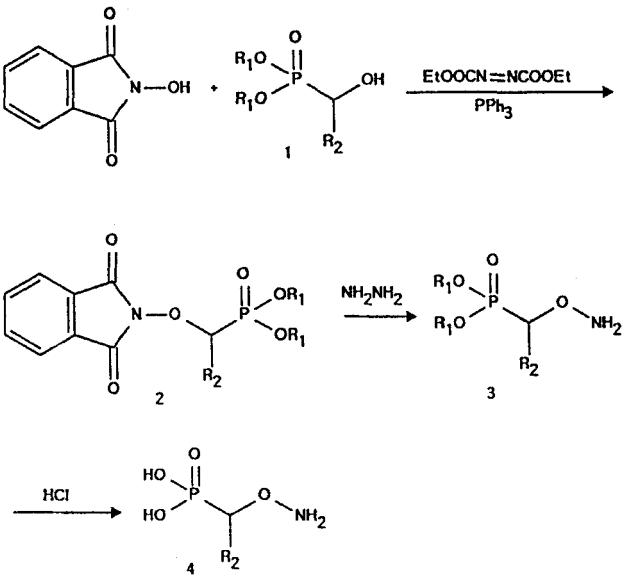
Abstract The preparation, reactions, and biological activity of 1-aminooxyalkylphosphonic- and phosphinic acids and derivatives are reported.

Introduction

L-α-Aminooxy-ß-phenylpropionic acid is a potent competitive inhibitor of phenylalanine ammonia-lyase (PAL)[2] and aminooxyacetic acid is an efficient inhibitor of anthocyanin synthesis[2,3] and of γ-aminobutyric acid - α-ketoglutaric acid transaminase in vivo[4], but a relatively poor inhibitor of PAL.[5] Aminooxyacetic acid also reacts specifically with P-pyridoxal groups of cystathionase.[6] It seemed of interest to prepare the corresponding phosphonic and phosphinic acid analogs and to determine their biological activity.

RESULTS AND DISCUSSION

Two aminooxyalkylphosphonic acids have been described previously in the literature, e.i., aminooxymethylphosphonic acid[7,8] and ß-aminooxyethylphosphonic acid.[8] Whereas Denzel et al.[7] used the Mitsunobu reaction[9] to synthesize this type of compound, Khomutov et al.[8] prepared these compounds by the interaction of acethydroximic acid and ω-haloalkylphosphonates followed by hydrolysis. Because Mitsunobu's reaction is simple to carry out and gives satisfactory yields we used this method for the synthesis of several α-aminooxyalkylphosphonic acids (Scheme I).



Scheme I

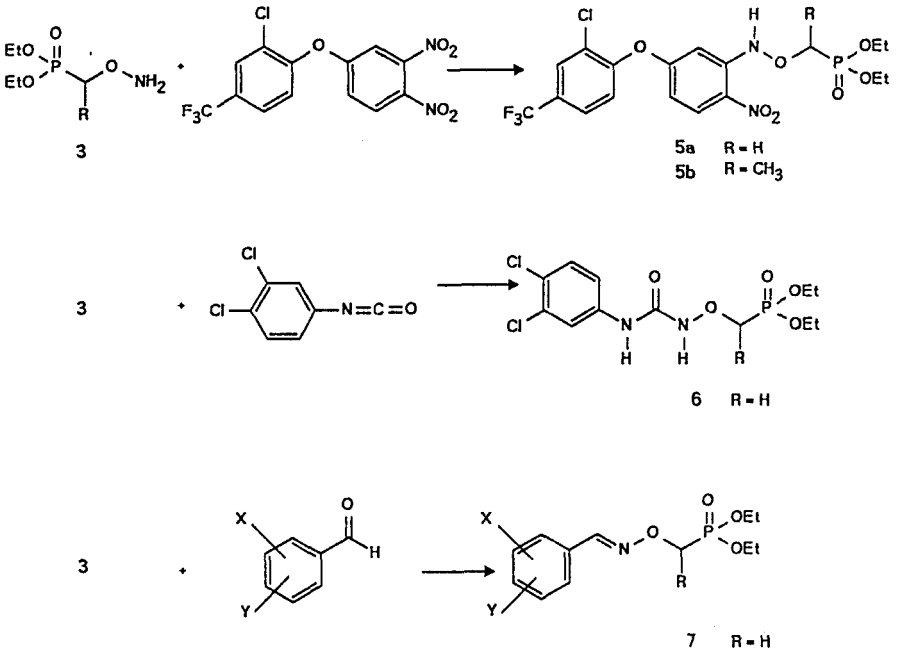
Furthermore this procedure is also useful for the synthesis of aminooxyalkylphosphonous and -phosphinic acids.[10]

α-Hydroxyalkylphosphonates, **1**, are easily obtained by the base catalyzed addition of aldehydes to secondary phosphites.[11] Condensation of **1** with N-hydroxyphthalimide under Mitsunobu's condition produces the 1-phthalimido-N-oxyalkylphosphonates **2** in yields ranging from 40 to 100 per cent. Treatment of **2** with hydrazine yields 1-aminooxyalkylphosphonates, **3**, in satisfactory yields.

Hydrolysis of **3** with 20% aqueous hydrochloric acid under reflux gives the crystalline 1-aminooxyalkylphosphonic acids, **4**, in good yield.

REACTIONS OF 1-AMINOOXYALKYLPHOSPHONATES

The 1-aminooxyalkylphosphonates, **3**, give all the reactions typical for O-alkylhydroxylamines. Thus the interaction of **3a** and 3,4-dinitro-2'-chloro-4'-trifluoromethyl-diphenyl ether gives O,O-diethyl-2-nitro-5-(2'-chloro-4'-trifluoromethylphenoxy)-phenyl-aminooxymethylphosphonate, **5a**, with isocyanates an urea derivative **6** is obtained, and oximes, **7**, are produced when **3** is treated with aldehydes or ketones (Scheme II). Dealkylation of **6**



Scheme II

and 7 with trimethylbromosilane followed by hydrolysis yields the corresponding acids (Table V).

BIOLOGICAL ACTIVITY

In contrast to 1-amino-2-phenylethylphosphonic acid[12], 1-aminooxy-2-phenylethylphosphonic acid, **4g**, is only a weak inhibitor of PAL[13], but the inhibition of anthocyanin synthesis in vivo by 1 mM of 1-aminooxy-3-phenylpropylphosphonic acid, **4i**, is 68%.[13] **4g** exhibits weak antifungal activity. More pronounced is the selective herbicidal activity of **5a** against dicotyledonous weeds in cereals and rice. At a concentration of 500 g/ha the control of seven dicotyledonous weeds was 79%; **5b** is less active (59%) than **5a**.

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