New synthesis and fungicidal activity of a phosphinic analogue of glycine

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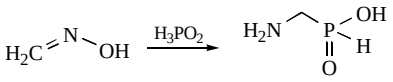
Aminomethylphosphinic acid, which was found to exhibit fungicidal activity, was synthesised in one step by the interaction of formaldoxime and sodium hypophosphite with HCl.

1-Aminoalkylphosphinic acids are of interest as biologically active isosteres of natural amino acids and as synthetic precursors of other organophosphorus analogues of amino acids.[1,2] Correspondingly, aminomethylphosphinic acid **1** can be considered an analogue of glycine, which is a metabolic precursor of a number of biologically active compounds: creatine (*N*-methylguanidoacetic acid), glutathione, and porphyrins. It was found that a phosphinic analogue of creatine can be the substrate of creatine kinase,[3] which is an important enzyme of muscular contraction; thus, such analogues are promising for the regulation of cell metabolism. Acid **1** suitably protected at the amino group and the phosphorus-containing moiety is a starting compound in the synthesis of aminoalkylphosphinic acids by alkylation.[4]

Compound **1** was prepared using several procedures;† one of them was the amination of inaccessible chloromethylphosphinic acid.[5] The reaction of 1,2,5-tribenzhydrylhexahydro-*s*-triazine with H_3PO_2 resulted in N-substituted compound **1**, which was converted into acid **1** in a total yield of 6%.[6] The use of the ethyl ester of diethoxymethylphosphinic acid in place of H_3PO_2 significantly increased the yield of compound **1**.[7] The interaction of another phosphorus-containing synthon, the bis(trimethylsilyl) ester of ethoxycarbonylphosphinic acid, with *N*-(bromomethyl)phthalimide followed by the hydrolysis of the resulting phthalimide derivative also resulted in an analogue of compound **1**.[8] Thus, the currently available procedures for the preparation of amino acid **1** include the syntheses of both amine and phosphorus components and are multistage processes.

A general procedure for the preparation of 1-aminoalkylphosphinic acids by the interaction of oximes with anhydrous H_3PO_2 is well known.[9,10] We studied this reaction and found that strong acids catalyse the reaction and water-free conditions are not critical for the reaction. This allowed us to exclude the preparation and use of anhydrous H_3PO_2, which is dangerous compound, especially at elevated temperatures. This practically resulted in a single-step procedure for the synthesis of amino acid **1** in ~25% yield. In this procedure, an aqueous solution of NaH_2PO_2 and formaldoxime (from aqueous formaldehyde and hydroxylamine) was added to hot HCl in alcohol, and the product was separated by ion-exchange chromatography (Scheme 1).

Some 1-aminoalkylphosphinic acids exhibit antibacterial activity[2] and inhibit the growth of leukemia cells L1210.[11] However, there is no published data on the biological activity of analogue **1**. We studied the effect of acid **1** on the growth of practically important phytopathogenic fungi and found that analogue **1** exhibited specific activity towards *Pyricularia oryzae*, a pathogen of rice. Procedures used for the cultivation of fungi and the evaluation of the effects of substances on the germination of conidia and mycelium and on pigmentation were described previously.[12] In *in vitro* experiments, the effects of analogue **1** were studied in both a standard agar medium and a medium containing only inorganic salts, glucose, thiamine, and biotine (a minimum medium) to reveal competition of the analogue with the amino acids of the medium. This procedure does not exclude a correlation between the activity under these conditions and *in vivo*. Acid **1** suppressed the growth of mycelium in a minimum medium (EC_{50} 50 μg cm^{-3}) and only slightly affected the germination of conidia. In a standard medium, the effect was weaker by an order of magnitude. Thus, acid **1**, similarly to glycine, can penetrate into a pathogen and compete with glycine in cell methabolism; this is responsible for the fungitoxicity of compound **1**.



1

Scheme 1

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† $NH_2OH{\cdot}HCl$ (7 g, 0.1 mol) and $NaHCO_3$ (7.5 g, 0.09 mol) were alternately added to an 8% aqueous formaldehyde solution (40 ml, 0.1 mol) with stirring to maintain pH 4–5. Next, the reaction mixture was stirred for 2 h; $NaH_2PO_2{\cdot}H_2O$ (21.2 g, 0.2 mol) was added, and resulted mixture was added to stirring 20% HCl (40 ml, 0.22 mol of HCl) in 50 ml of MeOH at reflux. The mixture was refluxed for 30 min, cooled, and evaporated in a vacuum. The residue was dissolved in 15 ml of water, and the product was separated on Dowex 50x8 resin (H^+ form); 15% aqueous isopropanol was used as an eluent. Fractions containing compound **1** were vacuum evaporated to dryness; the residue was vacuum dried over P_2O_5 to obtain compound **1** (2.4 g, 25%), mp 259–263 °C (decomp.) [lit., 254–256 °C;[6] 258–260 °C;[7] 272–276 °C[8] (decomp.)]. R_f 0.55 (Pr^iOH–25% NH_4OH–H_2O, 7:1:2). ^1H NMR (400 MHz, D_2O) δ: 2.88 (dd, 2CH, CH_2, J 11 Hz, J 1.9 Hz), 6.99 (dt, 1H, PH, J 540 Hz, J 1.8 Hz).