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A New Method for the Preparation of 2-Pyrrolidinylphosphinic Acid and Homologues.

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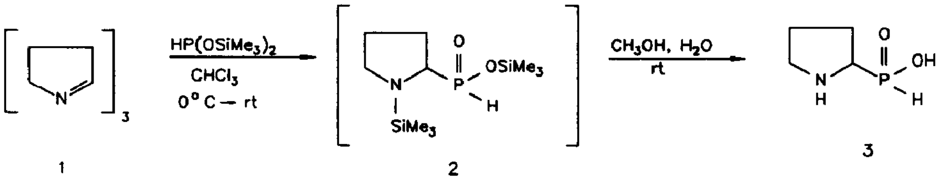
Abstract. *2-Pyrrolidinylphosphinic acid has been synthesized in a one pot reacion in 90% yield from 1-pyrroline trimer and bis(trimethylsilyl) phosphonite. The same procedure has been applied for the preparation of the piperidine and perhydroazepine homologues.*

1-Aminoalkylphosphinic acids are isosters of 1-aminoalkylcarboxylic acids and interesting compounds in the design of enzyme inhibitors. Inhibitors of angiotensine converting enzyme[1], D-Ala: D-Ala ligase[2], HIV-protease[3] and glutamine synthetase[4], characterized by an aminoalkylphosphinic acid moiety, are described.

The preparation of the phosphinic acid analogue of proline **3**, an important intermediate in the synthesis of potential enzyme inhibitors has already been described by Baylis and coworkers[5]. This compound was synthesized using a general method for the synthesis of 1-aminoalkylphosphinic acids by addition of 4-hydroxybutanal to diphenylmethylamine hypophosphite (yield 42 %), bromination and hydrolysis with HBr (yield 61 %) and cyclization with base in a two-phase system (yield 74 %).



We report a high yield, one pot method to prepare **3**. The 1-pyrroline trimer **1**[6], prepared from pyrrolidine by silver-catalyzed oxidation with sodium persulphate, already used for the synthesis of the phosphonic acid analogue of proline[7], is used as starting material. Reaction with bis(trimethylsilyl) phosphonite[8,9] and treatment of the obtained *N,O*-(bistrimethylsilyl) 2-pyrrolidinylphosphinate **2** with aqueous methanol affords 2-pyrrolidinylphosphinic acid **3**[10] in 90 % yield.

The same method, starting from piperidine[11] and perhydroazepine, affords 2-piperidinylphosphinic acid[12] (22 % yield) and 2-perhydroazepinylphosphinic acid[13] (27 % yield), respectively.

General procedure for the preparation of **3**.

Chloroform (10 ml) was added from a syringe to the *in situ* generated bis(trimethylsilyl) phosphonite (37.2 mmol) at 0 °C under nitrogen and stirring was continued for 15 minutes. A solution of 1-pyrroline trimer **1** (2.65 g, 12.8 mmol) in chloroform (25 ml) was gradually injected at 0 °C into the solution and stirring was continued at ambient temperature for 12 hours. The solvent is evaporated under reduced pressure and the resulting mixture dissolved in methanol (20 ml) and water (5 ml) and stirred for 5 hours. The solvent was removed under reduced pressure and the practically pure oily **3** chromatographed on silicagel (10-40 µm) with methanol-water (4:1) to give 4.6 g (90 % - according to bis(trimethylsilyl) phosphonite) as a light yellow oil which crystallized in methanol-ether.

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10. **IR** (KBr): 3400 (OH), 3000-2400 (NH_2^+), 2295 (P-H); 1625 (NH_2^+), 1450, 1410, 1200-1180 (P=O); 1050 (P-O), 960, 935, 750 cm^{-1}; **^{31}P-NMR** (D_2O-TSP, δ): 18.82; **^{1}H-NMR** - 400 MHz (D_2O-TSP, δ): 2.01-2.16 (1H,2H, m, H-3,H-4), 2.23-2.30 (1H, m, H-3), 3.39 (2H, t, H-5), 3.49-3.55 (1H, m, H-2), 7.07 (1H, dd, $^1J_{PH}$=538 Hz, $^3J_{HH}$=1.7 Hz, PH); **MS-FAB** (M + H^+): 136.
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12. **IR** (KBr): 3420 (OH), 2940-2480 (NH_2^+), 2300 (P-H); 1620 (NH_2^+), 1450, 1190 (P=O); 1060 (P-O), 975, 760 cm^{-1}; **^{31}P-NMR** (D_2O-TSP, δ): 19.41; **^{1}H-NMR** - 300 MHz (D_2O-TSP, δ): 1.45-2.10 (2H,2H,2H, m, H-3,H-4,H-5), 2.95-3.15 (2H, m, H-6), 3.40-3.50 (1H, m, H-2), 6.94 (1H, dd, $^1J_{PH}$=537 Hz, $^3J_{HH}$=1.5 Hz, PH); **MS-FAB** (M + H^+): 150.
13. **IR** (KBr): 3420 (OH), 2920-2480 (NH_2^+), 2280 (P-H); 1620 (NH_2^+), 1450, 1180 (P=O); 1050 (P-O), 1000, 970, 800, 750 cm^{-1}; **^{31}P-NMR** (D_2O-TSP, δ): 20.59; **^{1}H-NMR** - 300 MHz (D_2O-TSP, δ): 1.57-1.64 (2H, m, H-5), 1.80-1.98 (1H,2H,2H, m, H-3,H-4,H-6), 2.13-2.25 (1H, m, H-3), 3.16-3.48 (3H, m, H-2, H-7), 6.99 (1H, dd, $^1J_{PH}$=534 Hz, $^3J_{HH}$=1.5 Hz, PH); **MS-FAB** (M + H^+): 164.

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