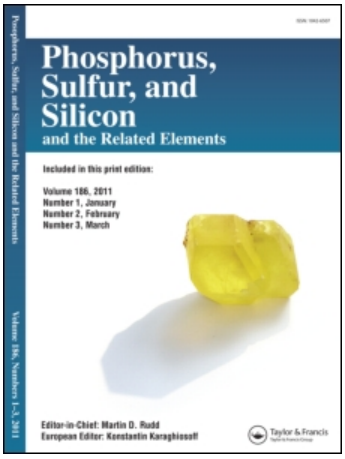

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SYNTHESIS AND CHARACTERIZATION OF OXIMINO PYRIDOYL PHOSPHONATES

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SYNTHESIS AND CHARACTERIZATION OF OXIMINO PYRIDOYL PHOSPHONATES

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Oximino pyridoyl phosphonates were synthesised as well as the methiodide of oximino-2-pyridoyl phosphonate. All these compounds along with their intermediates have been characterized by spectroscopic methods and by elemental analysis.

Key words: Phosphite, Michaelis-Becker reaction, Oximino pyridoyl phosphonates.

INTRODUCTION

Standard therapy for organophosphorus poisoning is based on the co-administration of atropine and a reactivator.[1,2] It is recognised that the reactivation occurs through the initial formation of a reactivator-enzyme complex followed by replacement of the phosphoryl group from the acetylcholinestrase enzyme.[3,4a,b] In this regard, compounds featuring the oximino (=NOH) function have received maximum attention, the standard drug being 2-[(hydroxyimino)methyl]1-methyl pyridinium halide (2-PAM).[5]

We felt that introduction of the diethyl phosphite function adjacent to the oximino group would not only increase the nucleophilicity of the latter, because of the possibility of hydrogen bonding, but also increase the lipophilicity to some extent. In order to test this proposition, we report the synthesis and characterization of oximino pyridoyl phosphonates, which are essentially 2-PAM analogues and are described in this paper.

RESULTS AND DISCUSSION

The synthesis of aroylphosphonate oximes has already been reported in the literature.[6] This was through the reaction of the aroyl phosphonate with hydroxylamine hydrochloride. In order to synthesise pyridoyl phosphonate and its oximes, the above route was thought to be the most convenient. However, during the preparation of pyridoyl phosphonates, we encountered some unusual reactions which have already been reported.[7] Syntheses of the required phosphonate oximes were accomplished through a different route.

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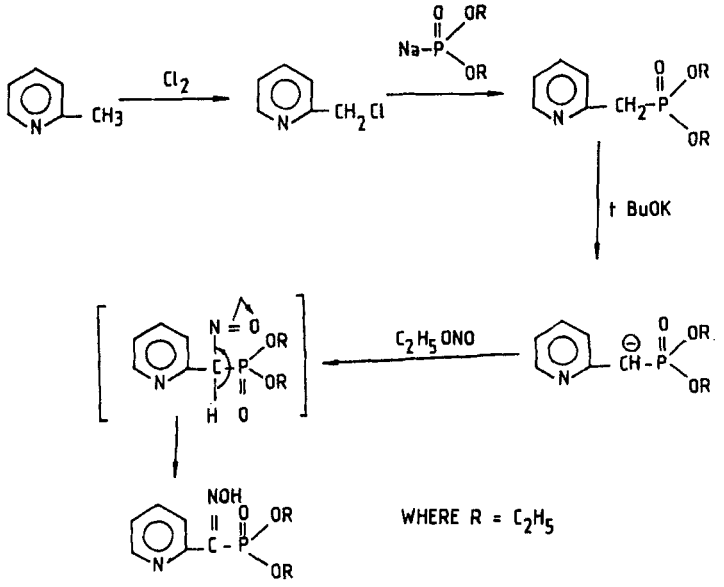
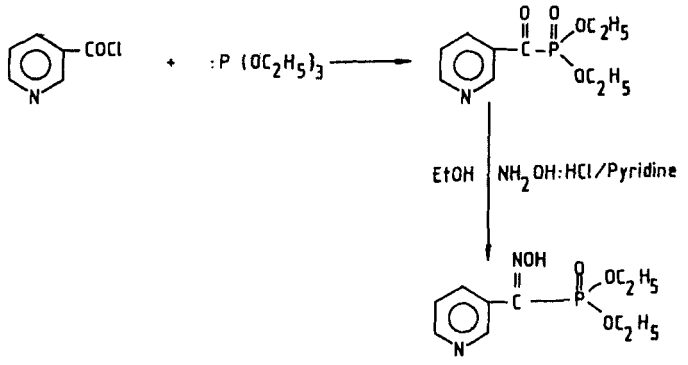
2-Picoline was chlorinated in the side chain with chlorine in the presence of sodium bicarbonate following the method of Mathes and Schuly.[8] The 2-chloromethyl pyridine underwent a Michaelis Becker reaction with the sodium salt of diethylphosphite. The reaction was almost quantitative and the product was homogenous on t.l.c. Diethyl 2-pyridyl methylphosphonate was characterized by IR, ^{1}H n.m.r. and mass spectroscopy (see experimental section). The methylene group of the above phosphonate is flanked by a pyridyl ring and a phosphonate group and therefore, a carbanion generation at the methylene centre was a reasonable proposition. A strong and bulkier base, potassium *t*-butoxide was used. During the addition of the base there was an intense color change from yellow to yellowish-brown and the *t*-butoxide dissolved completely in the ether. Ethyl nitrite was used as a nitrosoating agent. The reaction was rapid and gave rise to two products. The products were separated by column chromatography. The fast moving component was rejected as it did not contain a phosphonate group at all. The second component was the required oximino-2-pyridoyl phosphonate. The mechanism has been shown in Scheme I. The compound was characterized by its elemental analysis and by IR, ^{1}H nmr and mass spectral data.

The methiodide of the above compound was made by refluxing the oxime with excess of methyl iodide in chloroform. The solid product gave the correct elemental analysis for nitrogen and phosphorus. The IR spectrum had absorption at 1250 and 1210 cm^{-1} for the phosphonate group in addition to strong hydroxyl absorption. With silver nitrate solution it gave a yellow precipitate, showing the presence of iodide ion.

The preparation of oximino-3-pyridoylphosphonate was straight forward. Approximately 18% of 3-pyridoyl phosphonate obtained by the reaction of nicotinoyl chloride with triethyl phosphite was converted into its oxime following the method



SCHEME I



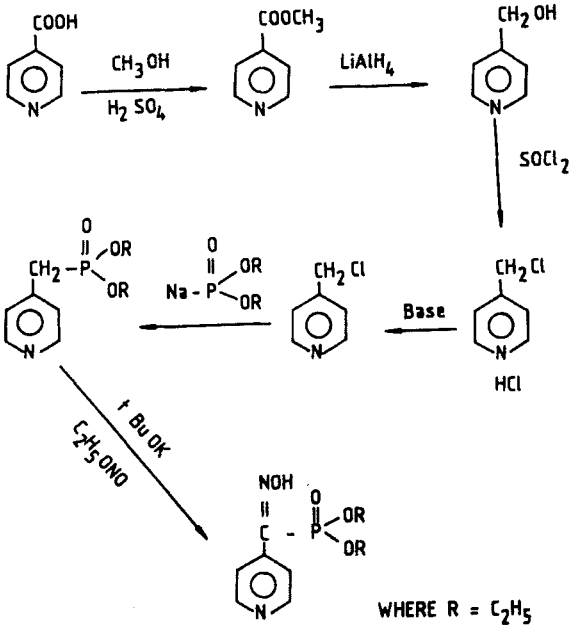
SCHEME II

of Berlin and Coworkers.[6] The compound was pure on t.l.c. and gave the correct elemental analysis. Strong and broad IR absorption at 3050 cm^{-1} confirmed the presence of a hydroxyl group. Furthermore, peaks at 1250 cm^{-1} and 1020 cm^{-1} and the absence of peaks at 1650 cm^{-1} also established the structure. The mass spectrum of this compound had the molecular ion peak at 258. The reaction is shown in Scheme II.

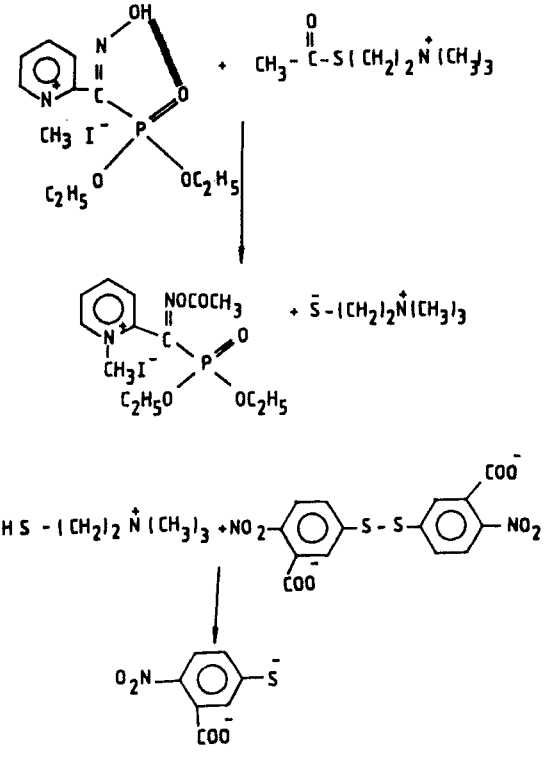
Since 4-chloromethyl pyridine could not be obtained by direct chlorination of 4-picoline, a longer route for its preparation was adopted. This involved the reduction of the methyl ester of isonicotinic acid with lithium aluminum hydride in ether which gave 4-hydroxymethylpyridine.[9] This, on treatment with thionyl chloride, formed 4-chloromethyl pyridine hydrochloride in almost quantitative yield. 4-Chloromethylpyridine, obtained after basification, was treated with the sodium salt of diethyl phosphite as in case of 2-derivative. The reaction has been shown in Scheme III.

The structure of the diethyl 4-pyridyl phosphonate[10] was confirmed on the basis of elemental analysis and spectral data. The oximino compound was obtained in a manner similar to the 2-derivative. This gave a complicated mixture from which only 20% of the required product was isolated and finally confirmed by IR ^1H n.m.r and mass spectral data. All of the above data were in conformity with the structure of diethyl 4-pyridyl phosphonate oxime.

In reactivation studies,[11] the enzyme was first inhibited with O—P compound and a calculated quantity of standard reactivator such as like 2-PAM was added. The complex was incubated for 30 min before the regular assay was done. For monitoring the reactivation ability of oximino-2-pyridoylphosphonate methiodide, the phosphorylated enzyme was incubated with the above methiodide in a proportion which was equivalent to that of the 2-PAM chloride which was also used as a control. The reactivation obtained for 2-PAM chloride under these conditions was about 30 to 35% of the original enzyme activity. Though 2-oximino pyridoyl phosphonate methiodide increased the rate of formation of thiophenolate anion; the control experiment proved that the enhanced production was a result of chemical reaction and not due to reactivation of the enzyme. Possibly the chemical reaction follows the mechanism shown in Scheme IV. In view of the above results



SCHEME III



SCHEME IV

oximino-3-pyridoylphosphonate and oximino-4-pyridoyl phosphonate assays were not attempted.

EXPERIMENTAL

Materials: 2-Picoline, diethylphosphite, methyl iodide hydroxylamine hydrochloride, isonicotinic acid, nicotinic acid, lithium aluminum hydride (Aldrich) were used as received. Thionyl chloride, pyridine, ethanol and *t*-butyl alcohol were used after distillation. Lypophilized electrical AChE was used with a normal activity of 1.4×10^3 Ach units per milligram. 5,5'-Dithiobis (2-nitrobenzoic acid) (DTNB) and acetylthiocholine were used as supplied by Sigma Chemical Co. Diisopropylfluorophosphate (DFP) was synthesised in our laboratory. Ethyl nitrite was freshly prepared by following the method of Semon and Damerll.[12] Instrumental: IR spectra were run neat on KBr disks on a Perkin-elmer 577 spectrophotometer, NMR spectra were recorded on a Perkin-Elmer R-32 instrument operating at 90 MHZ with TMS as an internal standard. Mass spectra were obtained on Jeol-Dx-300 mass spectrometer. Elemental analyses were performed on a Carlo-Erba elemental analyzer Model 1106.

Diethyl 2-pyridylmethyl phosphonate: 2-Chloromethyl pyridine 25.7 g (0.2 mol) was slowly added to a stirred mixture of 4.6 g (0.2 mol) of sodium in benzene and 30.4 g (0.22 mol) of diethylphosphite and the mixture was refluxed for 30 min. The mixture was cooled, filtered and the benzene layer was washed with water, dried ($MgSO_4$) and the solvent was evaporated to give the product. Yield 32.2 g (70%) bp 130° (2 mm); IR ν cm^{-1} 1590, 1240, 1020; NMR ^1H ($CDCl_3$) δ 8.58 (1H, d, J = 7 Hz), 7.7 (1H, t, J = 8 Hz); 7.42 (1H, d, J = 7 Hz), 7.2 (1H, m) 4.1 (4H, J = 8 Hz); 3.45 (2H, d, J = 20 Hz); 1.27 (6H, t); MS m/z 229. Analysis: [calculated (found)] N, 6.11 (5.77).

4-Chloromethylpyridine: Ethyl isonicotinate 27.4 g (0.2 mol) was treated with lithium aluminum hydride 11.4 (0.3 mol) in anhydrous ether. The reaction mixture was stirred for 30 min, hydrolysed with water (35 mL), and extracted with ether. 4-Hydroxymethyl pyridine[9] was obtained after evaporating the ether; yield 8.1 g (38%). 4-Hydroxymethylpyridine 8.1 g (0.074 mol) was treated with a 3 fold excess of thionyl chloride, and refluxed for 3 hrs. The excess $SOCl_2$ was removed and the residue was distilled to give 4-chloromethylpyridine; yield 8 g (83%).

Diethyl 4-pyridylmethyl phosphonate: To a stirred suspension of 1.18 g (0.05 mol) of sodium in benzene (30 ml) was added dropwise 7.8 g (0.05 mol) of diethyl phosphite and the mixture was refluxed for 30 min. To this was added a solution of 4-chloromethylpyridine; 6.5 g (0.05 mol) in benzene (20 ml). The mixture was stirred for another 30 min, cooled and filtered. The benzene layer was washed with water, dried ($MgSO_4$) and the solvent was evaporated to yield a pure product. Yield 7.5 g (64%); bp 140° (2.5 mm); IR ν cm^{-1} 1250, 1025; NMR ^1H ($CDCl_3$) δ 8.55 (2H, d, J = 7 Hz) 7.27 (2H, m), 4.1 (4H, m), 3.15 (2H, d, J = 33 Hz), 1.25 (6H, t); MS m/z 229, 92. Analysis: [calculated (found)] N, 6.11 (6.43).

Diethyl 3-pyridoyl phosphonate: 3-Pyridoyl chloride 14.1 g (0.1 mol) was placed in a 250 mL two-necked RB flask fitted with a reflux condenser and a $CaCl_2$ guard tube. Triethyl phosphite, 16.6 g (0.1 mol), was added at 0°C and the reaction mixture was stirred for 30 min at 0°C and then for 1 hr at room temperature. A yellow color developed in the beginning but turned intense brown after complete addition of the triethyl phosphite. The viscous product obtained was extracted with ether. The ether was evaporated, and the liquid residue was distilled to give a pure product; yield 4.37 g (18%) bp 128° (2 mm); IR ν cm^{-1} 1650, 1250, 1000, NMR ^1H ($CDCl_3$) δ 9.42 (1H, bs), 8.85 (1H, dd, J = 7 Hz) 8.55 (1H, dt, J = 8 Hz, 1 Hz), 7.48 (1H, dd, J = 8 Hz, 7 Hz) 4.3 (4H, q); 1.3 (6H, t); MS m/z 243, 154, 137, 109, 106. Analysis: [calculated (found)] C, 49.38 (49.01); H, 5.76 (5.46) N, 5.76 (5.46).

Diethyl 2-Pyridoyl phosphonate oximes: Hydrochloride salt. Diethyl 2-pyridylmethyl phosphonate 22.9 g (0.1 mol) was added slowly to a mixture of dry ether 100 ml and potassium *t*-butoxide 16 g (0.15 ml) maintaining the temperature below 0°C. An intense yellow color was formed during the addition of the phosphonate. The mixture was stirred till the potassium *t*-butoxide went into solution. Ethyl nitrite 15.0 g (0.2 mol) was added to the reaction mixture. During the course of addition, the color of the solution changed from yellow to yellowish brown. After the addition was complete the reaction mixture was stirred for 15 min. and then worked up by adding water (40 mL). The aqueous mixture was acidified with dilute HCl until the pH of the solution was about 7 then it was extracted with three 50 mL portions of ether. The organic layers were combined and dried ($MgSO_4$). The ether was evaporated and the residue was chromatographed on a silica gel column (10% acetone in benzene), yield 12.4 g (48.4%). The oxime was dissolved in dry ether and dry HCl was passed in to the mixture. A white precipitate was formed, filtered, washed with ether and dried, mp 125°C. IR ν cm^{-1} 3000, 1580, 1240, 1010; NMR

$^1H(CDCl_3)$ δ 8.65 (1H, d, J = 7 Hz); 7.7 (1H, m); 7.5 (1H, d, J = 7 Hz); 7.2 (1H, m) 4.12 (4H, q); 1.3 (6H, t); MS of a free base; m/z 258, 121. Analysis: [calculated(found)] C, 40.88 (41.00) H, 5.1 (5.36) N, 9.51 (9.76).

Diethyl 3-Pyridoyl phosphonate oxime: This was prepared following the method of Berlin *et al.*[6] Diethyl 3-pyridoyl phosphonate 12.1 g (0.05 mol) was slowly added (dropwise at such a rate so as to maintain the temperature of the slightly exothermic reaction below 30°C) to a mixture of 200 mL of absolute ethanol, 4.62 g (0.067 mol.) of hydroxylamine hydrochloride, and 5.91 g (0.075 mol) of pyridine. After the usual workup the syrup obtained was chromatographed to give a pure product, yield 6.0 g (39%) IR ν cm^{-1} 3050, 1250, 1020; NMR ^1H ($CDCl_3$) δ 8.54 (2H, d, J = 8 Hz) 7.25 (2H, m) 4.2 (4H, m) 1.25 (6H, t); MS m/z 258, 121. Analysis: [Calculated (found)] C, 46.51 (46.82) H, 5.81 (6.13) N, 10.8 (11.12).

Diethyl 4-Pyridoylphosphonate oxime: By following the method used to prepare diethyl 2-pyridoyl-methyl phosphonate oxime given above, diethyl 4-pyridoyl phosphonate oxime was prepared; yield 6.2 g (24%); IR ν cm^{-1} 1250, 1025; NMR ^1H ($CDCl_3$) δ 8.55 (2H, d, J = 7 Hz); 7.27 (2 H, m) 4.1 (4H, m) 1.25 (6H, t); MS m/z 258, 121. Analysis: [calculated (found)] C, 46.51 (46.73) H, 5.81 (5.96) N, 10.8 (11.12).

2-Pyridoyl phosphonate oxime: Methiodide. Diethyl 2-pyridoyl phosphonate oxime (2.58 gm (0.01 mol) and dry chloroform (40 ml) was placed in a 100 mL 2-necked RB flask which was placed in an ice salt mixture. Freshly distilled methyl iodide 2.82 g (0.02 mol) in dry chloroform (5 mL) was added dropwise and the mixture was stirred. The methyl iodide was added in 25–30 minutes. After complete addition of the methyl iodide, the mixture was stirred for 3 hrs at room temperature. The yellow precipitate was quickly filtered, washed first with dry $CHCl_3$ and then with dry ether. The presence of iodide ion was confirmed by a silver nitrate test which gave a pale yellow precipitate; yield 2.3 g (55%) IR ν cm^{-1} 3000, 1600, 1240, 1010. Analysis:[calculated (found)] C, 33.12 (33.32) H, 4.52 (4.86) N, 7.0 (6.65) P, 7.75 (8.01).

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