Syntheses of novel piperidin-4-ylphosphinic acid, and piperidin-4-ylphosphonic acid analogues of the inhibitory neurotransmitter 4-aminobutyric acid (GABA)

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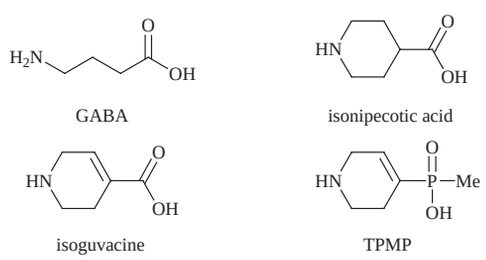
Received (in Cambridge) 16th June 1998, Accepted 11th August 1998

Piperidin-4-ylphosphinic acid, methyl(piperidin-4-yl)phosphinic acid and piperidin-4-ylphosphonic acid analogues of the $GABA_A$ agonist piperidin-4-ylcarboxylic acid (isonipecotic acid) were synthesised. The acid groups were introduced using a sequential Pudovik addition followed by a Barton deoxygenation procedure and finally followed by acidic hydrolysis. The mild and efficient procedure gave the target amino acids in good yields.

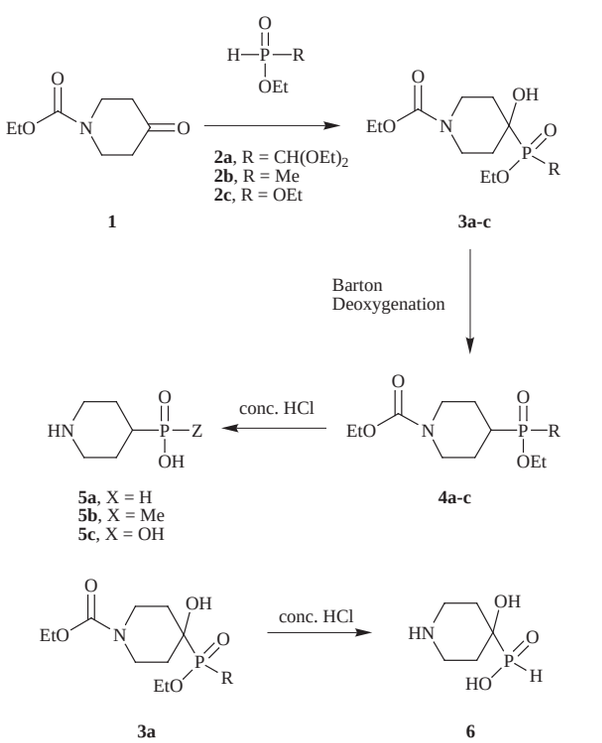
Introduction

The syntheses of phosphinic acids, methylphosphinic acids and phosphonic acids are currently an area of great interest due to the ability of these acids to function as effective bioisosteres of the carboxylic acid moiety in certain biological systems. Thus, very active compounds have been synthesised acting on a variety of different biological targets, including amino acid mimetics.[1–4] Phosphinic acid analogues with nanomolar receptor affinity of the inhibitory neurotransmitter 4-aminobutyric acid (GABA) have been reported[5,6] and phosphonic acid analogues of the excitatory amino acid glutamate have played an important role as pharmacological tools and potential therapeutic agents.[7] As part of our ongoing research on the GABA receptors[8] we wanted to investigate phosphorus acid based analogues of the $GABA_A$ agonist piperidin-4-ylcarboxylic acid (isonipecotic acid). Here we wish to describe the syntheses of piperidin-4-ylphosphinic acid, methyl(piperidin-4-yl)phosphinic acids and piperidin-4-ylphosphonic acid as novel analogues of isonipecotic acid. Recently methyl (1,2,3,6-tetrahydropyridin-4-yl)phosphinic acid (TPMPA), an analogue of the $GABA_A$ agonist 1,2,3,6-tetrahydropyridin-4-ylcarboxylic acid (isoguvacine), was found to be a relatively potent and very selective antagonist for the $GABA_C$ receptor.[9]



Results and discussion

The most common way of synthesising phosphinic and phosphonic acids is *via* the Michaelis–Arbuzov reaction between an alkyl halide and a trialkyl phosphite or dialkyl phosphonite.[1] However, the Michaelis–Arbuzov reaction involves nucleophilic substitution of the S_N2-type at the alkyl halide so that low yields and side reactions are often seen when non-activated and sterically hindered alkyl halides are used.[1] We therefore decided to develop another method for the synthesis of the isonipecotic acid analogues **5a**–**c** and **6**. The syntheses are outlined in Scheme 1. Base catalysed Pudovik addition of the phosphinates



Scheme 1 Syntheses of the piperidin-4-ylphosphinic acids, **5a** and **6**, methyl(piperidin-4-yl)phosphinic acid, **5b** and piperidin-4-ylphosphinic acid, **5c**.

2a,[3,10] **2b**[11,12] or diethyl phosphonate **2c** to piperidine **1** gave the respective hydroxyphosphinates **3a**, **3b** and the hydroxyphosphonate **3c**, all nicely crystalline compounds which were readily purified by recrystallisation. A radical deoxygenation procedure was used to remove the hydroxy functionality. We were not able to use the classical Barton deoxygenation[13] because the sterically hindered tertiary alcohols **3a**–**c** could not be converted to the corresponding thionocarbonates. However,

3a–**c** were smoothly converted to methyl oxalate esters which were readily deoxygenated using tributyltin hydride–AIBN.[14] The slightly hygroscopic phosphinates **4a**, **4b** and the phosphonate **4c** are liquids and were purified by flash chromatography. Complete deprotection was effected by refluxing in concentrated HCl to give, after recrystallisation, the pure hydrochloride products of **5a**–**c**. Deprotection of **3a** similarly gave the compound **6**.

In conclusion, we have synthesised the novel amino acids piperidin-4-ylphosphinic acid, methyl(piperidin-4-yl)phosphinic acid and piperidin-4-ylphosphonic acid, which are analogues of the $GABA_A$ agonist isonipecotic acid. The acids were synthesised using a tandem Pudovik addition followed by a modified Barton deoxygenation procedure and acidic hydrolysis. The mild and efficient procedure gave the acids in good yields. The acids are currently being evaluated for their biological properties.

Experimental

Preparation of 3a–c

N-Ethoxycarbonyl-4-piperidone (8.6 g, 50 mmol), the ethyl phosphinate **2a** (9.8 g, 50 mmol), **2b** (5.4 g, 50 mmol) or diethyl phosphonate **2c** (6.9 g, 50 mmol) and anhydrous triethylamine (7.0 ml, 50 mmol) were heated under nitrogen to 100 °C for 2 h (**2a** and **2c**) or 24 h (**2b**). The mixture was cooled to 30 °C and anhydrous diethyl ether (40 ml) added with stirring. The mixture was cooled to 0 °C. The colourless crystals formed were filtered, washed with anhydrous diethyl ether (2 × 6 ml) and dried *in vacuo*.

Ethyl (diethoxymethyl)(*N*-ethoxycarbonyl-4-hydroxypiperidin-4-yl)phosphinate 3a. Yield: 13 g (71%), mp 94–95 °C (Found: C, 49.15; H, 8.00; N, 3.86. $C_{15}H_{30}NO_7P$ requires C, 49.04; H, 8.23; N, 3.81%); δ_P(36.2 MHz, $CDCl_3$) 36.6; δ_H(400 MHz, $CDCl_3$) 4.85 [d, $^2J_{HP}$ 9, 1H, $(EtO)_2CHP$], 4.18 (dq, $^3J_{HP}$ 8, $^3J_{HH}$ 7, 2H, CH_2OP), 4.08 [q, $^3J_{HH}$ 7, 2H, $CH_2OC(O)N$], 3.87 (br s, 1H, OH), 3.80 (m, 2H, 2 × $CH_{eq}N$), 3.75 (m, 2H, CH_2O), 3.60 (m, 2H, CH_2O), 3.18 (m, 2H, 2 × $CH_{ax}N$), 1.90–1.80 (m, 4H, 2 × CH_2), 1.27 (t, $^3J_{HH}$ 7, 3H, CH_3), 1.22 (t, $^3J_{HH}$ 7, 3H, CH_3), 1.19 (t, $^3J_{HH}$ 7, 6H, 2 × CH_3); δ_C(100 MHz, $CDCl_3$) 155.3, 100.8 [d, $^1J_{PC}$ 133, $(EtO)_2CHP$], 70 [d, $^1J_{PC}$ 105, C(OH)P], 66.0 (d, $^3J_{PC}$ 7, CH_2O), 65.5 (d, $^3J_{PC}$ 9, CH_2O), 62.5 (d, $^2J_{PC}$ 8, CH_2OP), 61.1 (CH_2O), 38.0 (d, $^3J_{PC}$ 10, CH_2N), 30.8 (CH_2), 16.6 (d, $^3J_{PC}$ 5, CH_3), 15.1, 15,0, 14.6; *m*/*z* (FAB^+-MS) 368.2 ($M + H^+$, calc. 368.2).

Ethyl (*N*-ethoxycarbonyl-4-hydroxypiperidin-4-yl)methylphosphinate 3b. Yield: 10.6 g (76%), mp 101–102 °C (Found: C, 47.34; H, 7.95; N, 4.98. $C_{11}H_{22}NO_5P$ requires C, 47.31; H, 7.94; N, 5.02%); δ_P(36.2 MHz, $CDCl_3$) 53.40; δ_H(400 MHz, $CDCl_3$) 5.18 (br s, 1H, OH), 4.07 [q, $^3J_{HH}$ 6, 2H, $CH_2OC(O)N$], 4.03 (dq, $^3J_{HP}$ 3, $^3J_{HH}$ 7, 2H, CH_2OP), 3.95 (m, 2H, 2 × $CH_{eq}N$), 3.18 (app. t, J_{app} 13, 2H, 2 × $CH_{ax}N$), 1.90–1.50 (m, 4H, 2 × CH_2), 1.36 (2 d, $^2J_{HP}$ 13, 3H, CH_3P), 1.24 (t, $^3J_{HH}$ 7, 3H, CH_3), 1.19 (t, $^3J_{HH}$ 7, 3H, CH_3); δ_C(100 MHz, $CDCl_3$) 155.2, 69.3 [d, $^1J_{PC}$ 112, C(OH)P], 61.1 (d, $^2J_{PC}$ 8, CH_2OP), 61.0 (CH_2O), 38.0 and 37.9 (2 d, $^3J_{PC}$ 7, CH_2N), 30.8, 29.4, 16.4 (d, $^3J_{PC}$ 5, CH_3), 14.4, 8.6 (d, $^1J_{PC}$ 86, CH_3P); *m*/*z* (FAB^+-MS) 280.1 ($M + H^+$, calc. 280.1).

Diethyl (*N*-ethoxycarbonyl-4-hydroxypiperidin-4-yl)phosphonate 3c. Yield: 10.6 g (71%), mp 112–114 °C (Found C, 46.43; H, 7.61; N, 4.50. $C_{12}H_{24}NO_6P$ requires C, 46.6; H, 7.82; N, 4.53%); δ_P(36.2 MHz, $CDCl_3$) 24.4; δ_H(400 MHz, $CDCl_3$) 4.54 (br s, 1H, OH), 4.09 [q, $^3J_{HH}$ 7, 2H, $CH_2OC(O)N$], 4.04 (dq, $^3J_{HP}$ 3, $^3J_{HH}$ 7, 4H, 2 × CH_2OP), 3.90 (m, 2H, 2 × $CH_{eq}N$), 3.25 (m, 2H, 2 × $CH_{ax}N$), 1.85–1.70 (m, 4H, 2 × CH_2), 1.25 (t, $^3J_{HH}$ 7, 6H, 2 × CH_3), 1.19 (t, $^3J_{HH}$ 7, 3H, CH_3); δ_C(100 MHz, $CDCl_3$) 155.3, 68.8 [d, $^1J_{PC}$ 171, C(OH)P], 62.8 (d, $^2J_{PC}$ 8, CH_2OP), 61.1 (CH_2O), 38.0 (d, $^3J_{PC}$ 11, CH_2N), 31.0, 16.4 (d, $^3J_{PC}$ 5, CH_3), 14.6; *m*/*z* (FAB^+-MS) 310.3 ($M + H^+$, calc. 310.1).

Preparation of 4a–c

Ethyl (*N*-ethoxycarbonyl-4-hydroxypiperidin-4-yl)alkylphosphinate **3a** (5.5 g, 15 mmol), **3b** (4.2 g, 15 mmol), or the phosphonate **3c** (4.6 g, 15 mmol) and 4-*N*,*N*-dimethylaminopyridine (3.3 g, 27 mmol) were dissolved in dry MeCN (100 ml) under nitrogen, cooled to 0 °C (ice–water bath) and methyl oxalyl chloride (2.8 g, 22.5 mmol) was added dropwise under nitrogen *via* a syringe. The mixture was stirred under nitrogen at rt until ^{31}P NMR spectroscopy (generally a lowering of 5–7 ppm) and TLC showed complete esterification (30–90 min). The reaction mixture was diluted with EtOAc (400 ml), filtered, and the organic phase washed with saturated aqueous sodium hydrogen carbonate (2 × 70 ml), brine (70 ml), dried (anhydrous sodium sulfate) and evaporated *in vacuo* to a clear, light yellow oil. The oil was dissolved in dry toluene (140 ml), 1,1′-azoisobutyronitrile (0.68 g, 3.8 mmol) and tributyltin hydride (6.7 g, 22.5 mmol) added, and the reaction mixture heated to 90 °C under nitrogen for 3 h. The reaction mixture was evaporated *in vacuo*, and the oily residue purified by flash chromatography on silica gel ($6\frac{1}{2}$ × 13 cm) using MeOH–EtOAc–DCM (1:64:35; v/v/v) as eluent. Fractions containing the product were evaporated *in vacuo* to give the product as colourless oils.

Ethyl (diethoxymethyl)(*N*-ethoxycarbonylpiperidin-4-yl)phosphinate 4a. Yield: 3.1 g (60%); R_f = 0.36 (MeOH–DCM) (5:95; v/v) (Found: C, 50.08; H, 8.46; N, 4.04. $C_{15}H_{30}NO_3P·\frac{1}{2}H_2O$ requires C, 49.99; H, 8.67; N, 3.89%); δ_P(36.2 MHz, $CDCl_3$) 42.6; δ_H(400 MHz, $CDCl_3$) 4.72 [d, $^2J_{HP}$ 7, 1H, $(EtO)_2CHP$], 4.23 (m, 4H, CH_2OP + 2 × $CH_{eq}N$), 4.12 [q, $^3J_{HH}$ 7, 2H, $CH_2OC(O)N$], 3.87 (q, $^3J_{HH}$ 7, 2H, CH_2O), 3.69 (q, $^3J_{HH}$ 7, 2H, CH_2O), 2.73 (app. t, $J_{app.}$ 12, 2H, 2 × $CH_{ax}N$), 2.05 (m, 1H, CHP), 1.95 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.32 (t, $^3J_{HH}$ 7, 3H, CH_3), 1.27 (t, $^3J_{HH}$ 7, 3H, CH_3), 1.23 (t, $^3J_{HH}$ 7, 6H, 2 × CH_3); δ_C(100 MHz, $CDCl_3$) 155.4, 100.8 [d, $^1J_{PC}$ 138, $(EtO)_2CHP$], 65.6 (d, $^3J_{PC}$ 3, CH_2O), 65.5 (d, $^3J_{PC}$ 3, CH_2O), 61.7 (d, $^2J_{PC}$ 7, CH_2OP), 61.3 (CH_2O), 43.9 (d, $^3J_{PC}$ 14, CH_2N), 33.8 [d, $^1J_{PC}$ 93, C(OH)P], 24.3 (d, $^2J_{PC}$ 4, CH_2), 16.7 (d, $^3J_{PC}$ 5, CH_3), 15.1, 15.0, 14.7; *m*/*z* (FAB^+-MS) 352.1 ($M + H^+$, calc. 352.2).

Ethyl (*N*-ethoxycarbonylpiperidin-4-yl)methylphosphinate 4b. Yield: 3.7 g (93%) (Found: C, 47.96; H, 8.19; N, 4.91. $C_{11}H_{22}NO_4P·0.75\ H_2O$ requires C, 47.74; H, 8.49; N, 5.06%); δ_P(36.2 MHz, $CDCl_3$) 54.1; δ_H(400 MHz, $CDCl_3$) 4.19 (m, 2H, 2 × $CH_{eq}N$), 4.05 (m, 2H, CH_2OP) 3.99 [m, 2H, $CH_2OC(O)N$], 2.65 (m, 2H, 2 × $CH_{ax}N$), 1.85 (m, 2H, CH_2), 1.75 (m, 1H, CHP), 1.48 (m, 2H, CH_2), 1.36 (d, $^2J_{HP}$ 11, 3H, CH_3P), 1.20 (m, 6H, 2 × CH_3); δ_C(100 MHz, $CDCl_3$) 154.8, 60.8 (CH_2O), 59.7 (d, $^2J_{PC}$ 7, CH_2OP), 43.4 (d, $^3J_{PC}$ 14, CH_2N), 36.4 (d, $^1J_{PC}$ 99, CHP), 24.3 (d, $^2J_{PC}$ 2, CH_2), 16.2 (d, $^3J_{PC}$ 3, CH_3), 14.2, 10.8 (d, $^1J_{PC}$ 89, CH_3P); *m*/*z* (FAB^+-MS) 264.1 ($M + H^+$, calc. 264.1).

Diethyl (*N*-ethoxycarbonylpiperidin-4-yl)phosphonate 4c. Yield: 2.9 g (67%) (Found: C, 47.96; H, 8.04; N, 4.59. $C_{12}H_{24}NO_5P·\frac{1}{2}H_2O$ requires C, 47.68; H, 8.34; N, 4.63%); δ_P(36.2 MHz, $CDCl_3$) 29.9; δ_H(400 MHz, $CDCl_3$) 4.10 (m, 2H, 2 × $CH_{eq}N$), 4.05 (m, 6H, 3 × CH_2O), 2.65 (m, 2H, 2 × $CH_{ax}N$), 1.80 (m, 2H, CH_2), 1.50 (m, 3H, CHP + CH_2), 1.25 (t, $^3J_{HH}$ 7, 6H, 2 × CH_3), 1.20 (t, $^3J_{HH}$ 7, 3H, CH_3); δ_C(100 MHz, $CDCl_3$) 155.0, 61.4 (d, $^2J_{PC}$ 7, CH_2OP), 61.0 (CH_2O), 43.4 (d, $^3J_{PC}$ 17, CH_2N), 33.7 (d, $^1J_{PC}$ 147, CHP), 24.9 (d, $^2J_{PC}$ 4, CH_2), 16.2 (d, $^3J_{PC}$ 6, CH_3), 14.4; *m*/*z* (FAB^+-MS) 294.1 ($M + H^+$, calc. 294.1).

Removal of protecting groups to give 5a–c and 6

Ethyl (*N*-ethoxycarbonylpiperidin-4-yl)alkylphosphinate **3a**, **4a,b** or the phosphonate **4c** (10 mmol) was dissolved in conc. HCl (50 ml) and the clear solution refluxed in an atmosphere of nitrogen for 20 h. The clear solution was evaporated *in vacuo* and co-evaporated twice with water (10 ml). The oily residue was redissolved in hot absolute EtOH (70 ml), cooled to rt and **5** and **6** were precipitated with diethyl ether, collected by filtration and dried under vacuum.

Piperidin-4-ylphosphinic acid hydrochloride 5a. Recrystallised from MeOH–diethyl ether. Hygroscopic. Stored over P_2O_5. Yield: 1.13 g (61%), mp 217–219 °C (Found: C, 31.77; H, 6.73; N, 7.31. $C_5H_{12}NO_2P{\cdot}HCl{\cdot}¼\ H_2O$ requires C, 31.59; H, 7.16; N, 7.37%); δ_P(36.2 MHz, H_2O, DMSO-d_6 ext. lock) 39.9 ($^1J_{PH}$ 476); δ_H(400 MHz, D_2O) 3.45 (m, 2H, 2 × $CH_{eq}N$), 2.95 (m, 2H, 2 × $CH_{ax}N$), 2.0 (m, 2H, CH_2), 1.85 (m, 1H, CHP), 1.6 (m, 2H, CH_2); δ_C(100 MHz, D_2O) 43.4 (d, $^3J_{PC}$ 11, CH_2N), 33.1 (d, $^1J_{PC}$ 96, CHP), 20.3; *m*/*z* (FAB^+-MS) 150.1 (M + H^+, calc. 150.1).

Methyl(piperidin-4-yl)phosphinic acid hydrochloride 5b. Recrystallised from absolute EtOH. Yield: 1.8 g (90%), mp 209–211 °C (Found: C, 36.29; H, 7.55; N, 7.04. $C_6H_{14}NO_2P{\cdot}HCl$ requires C, 36.10; H, 7.57; N, 7.02%); δ_P(36.2 MHz, H_2O, DMSO-d_6 ext. lock) 53.23; δ_H(400 MHz, D_2O) 3.45 (m, 2H, 2 × $CH_{eq}N$), 2.95 (m, 2H, 2 × $CH_{ax}N$), 2.10 (m, 2H, CH_2), 2.0 (m, 1H, CHP), 1.70 (m, 2H, CH_2), 1.40 (d, $^2J_{PH}$ 14, 3H, CH_3P); δ_C(100 MHz, D_2O) 43.4 (d, $^3J_{PC}$ 14, CH_2N), 33.6 (d, $^1J_{PC}$ 98, CHP), 21.2, 11.4 (d, $^1J_{PC}$ 89, CH_3P); *m*/*z* (FAB^+-MS) 164.0 (M + H^+, calc. 164.0).

Piperidin-4-ylphosphonic acid hydrochloride 5c. Recrystallized from EtOH–diethyl ether. Yield: 0.75 g (45%), mp 202–204 °C (Found: C, 30.21; H, 6.50; N, 6.95. $C_5H_{12}NO_3P{\cdot}HCl$ requires C, 29.79; H, 6.50; N, 6.95%); δ_P(36.2 MHz, H_2O, DMSO-d_6 ext. lock) 25.25; δ_H(400 MHz, D_2O) 3.40 (m, 2H, 2 × $CH_{eq}N$), 2.95 (m, 2H, 2 × $CH_{ax}N$), 2.10 (m, 2H, CH_2), 2.0 (m, 1H, CHP), 1.70 (m, 2H, CH_2); δ_C(100 MHz, D_2O) 43.4 (d, $^3J_{PC}$ 16, CH_2N), 31.7 (d, $^1J_{PC}$ 142, CHP), 22.2 (d, $^2J_{PC}$ 3); *m*/*z* (FAB^+-MS) 166.1 (M + H^+, calc. 166.1).

(4-Hydroxypiperidin-4-yl)phosphinic acid hydrochloride 6. Recrystallised from EtOH–diethyl ether. Yield: 1.6 g (80%), mp 194–195 °C (Found: C, 30.01; H, 6.34; N, 7.25. $C_5H_{12}NO_3P{\cdot}$HCl requires C, 29.79; H, 6.50; N, 6.95%); δ_P(36.2 MHz, H_2O, DMSO-d_6 ext. lock) 31.3 ($^1J_{PH}$ 517); δ_H(400 MHz, D_2O) 6.70 (d, $^1J_{HP}$ 517, 1H, HP), 3.25 (m, 2H, CH_2N), 3.18 (m, 2H, CH_2N), 1.90 (m, 2H), 1.80 (m, 2H); δ_C(100 MHz, D_2O) 66.4 [d, $^1J_{PC}$ 115, CH(OH)P], 38.2 (d, $^3J_{PC}$ 10, CH_2N), 26.0 (d, $^2J_{PC}$ 8); *m*/*z* (FAB^+-MS) 166.0 (M + H^+, calc. 166.0).

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Paper 8/04588G