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A convenient synthesis of 2-hydrazinoethylphosphonic acid and derivatives

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ABSTRACT

2-Hydrazinoethylphosphonic acid was prepared using a simple procedure involving Michael addition of hydrazine hydrate to diethyl ethenylphosphonate, followed by hydrolysis with hydrochloric acid. The product was converted into five- and six-membered heterocycles.

Hydrazinophosphonic acids, as analogues of aminophosphonic acids,[1] are of potential biological importance. For example, they have been demonstrated to protect cultivated plants from the phytotoxic action of herbicides.[2] Some synthetic approaches to hydrazinoalkylphosphonic acids have already been reported. Thus, 1-hydrazinoalkylphosphonic acids can be prepared by addition of diethyl phosphite to aldazines followed by subsequent acid hydrolysis.[3] Another method is based on the reaction of 1-sulfonyloxyalkylphosphonates with hydrazine hydrate.[4] 1-Hydrazino or 2-hydrazinoalkylphosphonic acids can also be prepared by selective reduction with sodium cyanoborohydride or with borane–tetrahydrofuran complexes of hydrazone derivatives prepared from 1-oxo or 2-oxophosphonates and subsequent hydrolysis of the resulting hydrazinoalkylphosphonates.[5] One example was presented in which the unstable monoammonium salt of 2-hydrazinoethyl-1,1-diphosphonic acid was prepared by addition of hydrazine hydrate to vinylidenediphosphonic acid. The method required heating in a sealed ampoule and the contaminated product was purified by chromatography.[6] Furthermore, Diels–Alder reaction of 1-diethoxyphosphorylbuta-1,3-diene and di-*tert*-butyl azodicarboxylate, followed by catalytic hydrogenation and hydrolysis steps, was shown to lead to 3-diethoxyphosphorylhexahydro-1,2-pyridazine.[7]

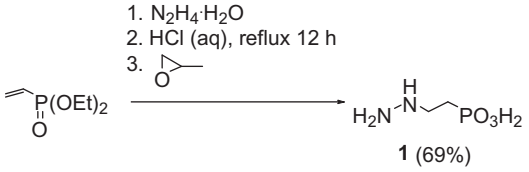
It has been shown that hydrazinoalkylphosphonates are useful building blocks for the synthesis of novel phosphonoalkyl heterocycles.[8] Considering the importance of azaheterocyclic phosphonates in medicinal[9] and coordination chemistry,[10] we recently reported a new strategy for the preparation of pyrazole-, thiazolidinone- and pyrrole-phosphonic acids.[11] Herein, we report a convenient method for the synthesis of 2-hydrazinoethylphosphonic acid; examples of its utilisation for the synthesis of phosphonoalkyl heterocycles are also given.

The synthetic route towards 2-hydrazinoethylphosphonic acid (**1**) is depicted in Scheme 1.

Commercial diethyl ethenylphosphonate (1 equiv) was added to hydrazine hydrate (20 equiv) and a mild exotherm was apparent. The mixture was stirred at room temperature for 24 h, then the unreacted hydrazine hydrate was distilled under reduced pressure (the recovered hydrazine hydrate can be reused). To remove any remaining traces of hydrazine hydrate the residue was evaporated with aqueous sodium hydroxide solution (2 equiv) and with water. Hydrolysis with hydrochloric acid (reflux 12 h) followed by treatment with propylene oxide provided the hydrazinophosphonic acid **1** in 69% yield.[12]

Condensation of compound **1** with various aromatic aldehydes or ketones resulted in the formation of stable hydrazone derivatives **2a–e** in good yields (Table 1).[13,14] However, attempts to prepare hydrazone derivatives from **1** and aliphatic aldehydes or ketones failed.

To the best of our knowledge, free hydrazinoalkylphosphonic acids have not been used for the synthesis of heterocycles.



Scheme 1. Synthesis of 2-hydrazinoethylphosphonic acid (**1**).

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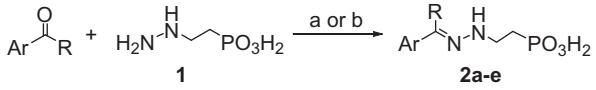
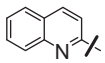
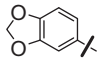
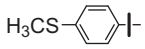
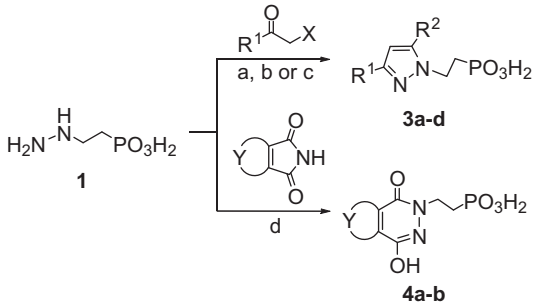
Table 1
Condensation of **1** with aromatic aldehydes and ketones



Entry	Ar	R	Product	Yield[c] (%)
1[a]		H	**2a**	79
2[a]		H	**2b**	92
3[a]		H	**2c**	88
4[b]	Ph	Me	**2d**	83
5[b]		Me	**2e**	67

[a] Reaction conditions: MeOH–H_2O, reflux 12 h.
[b] Reaction conditions: (i) $NaHCO_3$, MeOH–H_2O, reflux 12 h; (ii) HCl (aq).
[c] Isolated pure product.

Table 2
Synthesis of *N*-phosphonoethylheterocycles from **1**



Entry	X	Y	R^1	R^2	Product	Yield[e] (%)
1[a]	Ac	—	Me	Me	**3a**	56
2[a]	CO_2Et	—	Me	OH	**3b**	87
3[b]	CO_2Et	—	CF_3	OH	**3c**	32
4[c]	CN	—	Ph	NH_2	**3d**	67
5[d]	—		—	—	**4a**	56
6[d]	—		—	—	**4b**	90

[a] Reaction conditions: (i) $NaHCO_3$, H_2O–MeOH, reflux 15 min; (ii) concd HCl (aq); (iii) propylene oxide, MeOH.
[b] Reaction conditions: (i) $NaHCO_3$, H_2O, reflux 3 h; (ii) HCl (aq).
[c] Reaction conditions: (i) MeOH–H_2O, reflux 18 h.
[d] Reaction conditions: (i) Na_2CO_3, H_2O, reflux 15 min; (ii) HCl (aq).
[e] Isolated pure product.

Examples of the synthetic application of hydrazinophosphonic acid **1** for the preparation of azaheterocycles bearing a phosphonoalkyl moiety are shown in Table 2.[15–18]

Thus, hydrazinophosphonic acid **1** (entry 4) or its disodium salt (entries 1–3, 5 and 6) and cyanocarbonyl (entry 4) or dicarbonyl compounds (entries 1–3, 5 and 6) were refluxed in methanol–water or in water. After acidification, the products **3c** and **4a,b** were obtained (entries 3, 5 and 6). In the case of pyrazoles **3a,b** additional treatment with propylene oxide was required (entries 1 and 2). The aminopyrazole **3d** crystallised after concentration of the reaction mixture (entry 4). The structures of **3b–d** were confirmed by heteronuclear multiple bond correlation (HMBC) experiments in which the signal of the pyrazole carbon atom C-5 correlates with the signal of the methylene protons CH_2N.

Hydrazinohosphonic acid **1** and its heterocyclic derivatives **3a–d** and **4a,b** are crystalline stable compounds and can be stored at room temperature without decomposition. Their structures were confirmed by NMR, IR and elemental analyses.

In conclusion, we have developed a simple and convenient one-pot strategy for the preparation of a new hydrazinoethylphosphonic acid. The product **1** was shown be a useful synthon for the synthesis of five- and six-membered azaheterocyclic ethylphosphonic acids.

Acknowledgement

The author thanks R. Bartnik, Emeritus Professor for his keen interest and encouragement.

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12. *2-Hydrazinoethylphosphonic acid (**1**)*: Diethyl ethenylphosphonate (21.53 g, 0.131 mol) was added to $N_2H_4{\cdot}H_2O$ (131.3 g 2.623 mol) during which time a mild exotherm occurred. The mixture was stirred at rt for 24 h, then the unreacted hydrazine hydrate was distilled under reduced pressure. The residue was evaporated with NaOH/H_2O soln (2.0 mol/L, 131.0 mL) and with H_2O (3 × 330 mL), to remove any remaining traces of hydrazine hydrate. Then concd HCl (aq) solution (330 mL) was added and the mixture refluxed for 12 h. After evaporation of HCl, the residue was dissolved in MeOH (164 mL), filtered, and the filtrate treated with propylene oxide (20 mL) and left in a refrigerator for 24 h. The crude product (15.90 g, mp 186–196 °C) was dissolved in boiling H_2O (131 mL) and boiling MeOH/H_2O (4/1, 328 mL) was added. The pure product precipitated as colourless crystals (12.60 g, 69%, mp 204–206 °C): IR (KBr): 3309–2507 (NH, OH), 1630 (NH), 1516 (NH), 1142 (P=O), 924 (P–O) cm^{-1}; ^1H NMR (600 MHz, D_2O): δ = 1.91–1.99 (m, 2H, CH_2P), 3.27–3.34 (m, 2H, CH_2N); ^{13}C NMR (151 MHz, D_2O): δ = 24.1 (d, $^1J_{PC}$ = 131.9 Hz, CH_2P), 46.9 (CH_2N); ^{31}P NMR (243 MHz, D_2O): δ = 18.67; Anal. Calcd for $C_2H_9N_2O_3P$: C, 17.15; H, 6.48. Found: C, 17.21; H, 6.37.
13. *Synthesis of hydrazones **2a–c**; general procedure*: A mixture of **1** (0.70 g, 5.0 mmol) and aromatic aldehyde (5.0 mmol) in MeOH/H_2O (6/1, 35 mL) was refluxed and stirred for 12 h. The resulting precipitate was filtered and washed with H_2O (2 × 5 mL), MeOH (2 × 5 mL) and Et_2O (5 mL) and dried (90 °C, 2 h). *2-[(2-(2-Quinolylmethylene)hydrazino]ethylphosphonic acid (**2a**)*: Yield: 1.10 g (79%); colorless crystals: mp 211–214 °C. IR (KBr): 3424–2316 (OH, NH), 1657 (C=N), 1571, 1501, 1455, 1223 (P=O), 1122, 1027, 933 (P–OH) cm^{-1}; ^1H NMR (600 MHz, D_2O/NaOD): δ = 1.76–1.81 (m, 2H, CH_2P), 3.44–3.48 (m, 2H,CH_2N), 7.44–7.97 (m, 7H, CH_{arom}, CHN); ^{13}C NMR (151 MHz, D_2O/NaOD): δ = 28.1 (d, $^1J_{PC}$ = 126.8 Hz, CH_2P), 44.6 (CH_2N), 117.5 (CH), 126.7 (CH), 126.9 (CH), 127.4 (C_{arom}), 128.0 (CH), 130.3 (CH), 137.3 (CH), 137.4 (CH), 146.3 (C_{arom}), 154.1 (C_{arom}); ^{31}P NMR (243 MHz, D_2O/NaOD): δ = 18.59; Anal. Calcd for $C_{12}H_{14}N_3O_3P$: C, 51.62; H, 5.05. Found: C, 51.57; H, 4.98. 2-[(*2-(1,3-Benzodioxol-5-ylmethylene)hydrazino]ethylphosphonic acid (**2b**)*: Yield: 1.25 g (92%); colorless crystals: mp 196–198 °C; IR (KBr): 3447–2341 (OH, NH), 1629 (C=N), 1600, 1503, 1463, 1258 (P=O), 1145, 1021, 917 (P–OH) cm^{-1}; ^1H NMR (600 MHz, D_2O/NaOD): δ = 1.64–1.70 (m, 2H, CH_2P), 3.29–3.33 (m, 2H,CH_2N), 5.99 (s, 2H, CH_2O), 6.90–7.16 (m, 3H, CH_{arom}), 7.86 (s, 1H, CHN); ^{13}C NMR (151 MHz, D_2O/NaOD): δ = 28.3 (d, $^1J_{PC}$ = 127.0 Hz, CH_2P), 45.4 (CH_2N), 101.5 (CH_2O), 105.5 (CH_{arom}), 108.7 (CH_{arom}), 122.5 (CH_{arom}), 129.1 (C_{arom}), 145.0 (CHN), 147.8 (C_{arom}), 148.3 (C_{arom}); ^{31}P NMR (243 MHz, D_2O/NaOD): δ = 18.81; Anal. Calcd for $C_{10}H_{13}N_2O_5P$: C, 44.13; H, 4.81. Found: C, 44.02; H, 4.84.

*2-[2-[(4-Methylsulfanylphenyl)methylene]hydrazino]ethylphosphonic acid (**2c**)*: Yield: 1.20 g (88%); colorless crystals: mp 175–177 °C; IR (KBr): 3432–2333 (OH, NH), 1623 (C=N), 1595, 1227 (P=O), 1129, 1112, 1092, 1012, 940 (P–OH) cm^{-1}; ^1H NMR (600 MHz, D_2O/NaOD): δ = 1.65–1.71 (m, 2H, CH_2P), 2.49 (s, 3H, CH_3) 3.31–3.35 (m, 2H,CH_2N), 7.31–7.52 (m, 4H, CH_{arom}), 7.89 (s, 1H, CHN); ^{13}C NMR (151 MHz, D_2O/NaOD): δ = 14.4 (CH_3), 28.3 (d, $^1J_{PC}$ = 127.0 Hz, CH_2P), 45.3 (CH_2N), 126.3 (CH_{arom}), 127.1 (CH_{arom}), 131.6 (C_{arom}), 139.4 (C_{arom}), 144.3 (CHN); ^{31}P NMR (243 MHz, D_2O/NaOD): δ = 18.79; Anal. Calcd for $C_{10}H_{15}N_2O_3PS$: C, 43.79; H, 5.51. Found: C, 43.60; H, 5.42.

14. *Synthesis of hydrazones **2d**,**e**; general procedure*: A solution of **1** (1.40 g, 10.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in H_2O (10 mL) was refluxed for 1 min. Next, the dicarbonyl compound (13.0 mmol) and MeOH (30 mL) were added. The mixture was heated to 60 °C, and H_2O was added dropwise (to obtain a homogenous solution) which was refluxed for 12 h. The mixture was cooled and the solvent evaporated. The residue was dissolved in H_2O (10 mL) and extracted with Et_2O (3 × 50 mL). The aqueous phase was acidified with HCl (aq) solution (4 mol/L, 5 mL). The resulting precipitate was filtered and washed with H_2O (2 × 5 mL), cold MeOH (2 × 5 mL) and Et_2O (5 mL) and dried (90 °C, 2 h).

    2-[(2-(1-*Phenylethylidene)hydrazino]ethylphosphonic acid (**2d**)*: Yield: 2.00 g (83%); colorless crystals: mp 208–209 °C; IR (KBr): 3432–2337 (OH, NH), 1622 (C=N), 1447, 1245 (P=O), 1222, 1134, 1078, 918 (P–OH) cm^{-1}; ^1H NMR (600 MHz, D_2O/NaOD): δ = 1.69–1.74 (m, 2H, CH_2P), 2.18 (s, 3H, CH_3) 3.35–3.40 (m, 2H, CH_2N), 7.41–7.60 (m, 5H, CH_{arom}); ^{13}C NMR (151 MHz, D_2O/NaOD): δ = 14.2 (CH_3), 29.1 (d, $^1J_{PC}$ = 126.5 Hz, CH_2P), 46.7 (CH_2N), 126.4 (CH_{arom}), 128.7 (CH_{arom}), 129.0 (CH_{arom}), 139.2 (C_{arom}), 152.8 (C=N); ^{31}P NMR (243 MHz, D_2O/NaOD): δ = 19.13; Anal. Calcd for $C_{10}H_{15}N_2O_3P$: C, 49.59; H, 6.24. Found: C, 49.32; H, 6.14.

    *2-[2-[1-(2-Thienyl)ethylidene]hydrazino]ethylphosphonic acid (**2e**)*: Yield: 1.66 g (67%); colorless crystals: mp 216–218 °C; IR (KBr): 3439–2047 (OH, NH), 1605 (C=N), 1420, 1242 (P=O), 1220, 1131, 920 (P–OH) cm^{-1}; ^1H NMR (600 MHz, D_2O/NaOD): δ = 1.67–1.73 (m, 2H, CH_2P), 2.20 (s, 3H, CH_3) 3.33–3.37 (m, 2H,CH_2N), 7.08–7.40 (m, 3H, CH_{arom}); ^{13}C NMR (151 MHz, D_2O/NaOD): δ = 13.8 (CH_3), 29.0 (d, $^1J_{PC}$ = 127.1 Hz, CH_2P), 46.7 (CH_2N), 126.9 (CH_{arom}), 127.9 (CH_{arom}), 143.0 (C_{arom}), 147.6 (C=N); ^{31}P NMR (243 MHz, D_2O/NaOD): δ = 19.13; Anal. Calcd for $C_8H_{13}N_2O_3PS$: C, 38.71; H, 5.28. Found: C, 38.33; H, 5.29.

15. *Pyrazole derivatives **3a**,**b**: general procedure*: A soln of **1** (1.40 g, 10.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in H_2O (8 mL) was refluxed for 1 min. Next, the dicarbonyl compound (10.0 mmol) and MeOH (15 mL) were added and the mixture refluxed for 15 min. The mixture was cooled and the solvent was evaporated. The residue was dissolved in cold (−20 °C) concd HCl (aq) soln (30 mL) and left at this temperature for 1 h. The resulting precipitate of NaCl was removed by filtration, and HCl was evaporated under reduced pressure (0.5 mm Hg). The residue was dissolved in MeOH (30 mL), then filtered, and the filtrate treated with propylene oxide (3 mL). The mixture was left for 12 h. After evaporation of the solvent, the residue was stirred with MeOH/Et_2O (4/1, 20 mL) for 12 h. The resulting precipitate was filtered, washed with MeOH/Et_2O (4/1, 5 mL) and dried (90 °C, 2 h).

    *2-(3,5-Dimethylpyrazol-3-yl)ethylphosphonic acid (**3a**)*: Yield: 1.15 g (56%); white solid: mp 169–172 °C; IR (KBr): 3140–2346 (OH), 1265 (P=O), 1556, 1470, 1425, 1053, 969 (P–OH) cm^{-1}; ^1H NMR (600 MHz, H_2O/D_2O, 9/1): δ = 2.10–2.15 (m, 2H, CH_2P), 2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.36–4.41 (m, 2H,CH_2N), 6.24 (s, 1H, CH); ^{13}C NMR (151 MHz, H_2O/D_2O, 9/1): δ = 10.2 (CH_3), 10.4 (CH_3), 28.0 (d, $^1J_{PC}$ = 131.1 Hz, CH_2P), 43.7 (CH_2N), 107.4 (CH_{arom}), 145.9 (C_{arom}), 146.0 (C_{arom}); ^{31}P NMR (243 MHz, D_2O): δ = 18.37; Anal. Calcd for $C_7H_{13}N_2O_3P$: C, 41.18; H, 6.42. Found: C, 40.97; H, 6.47.
    *2-(5-Hydroxy-3-methylpyrazol-1-yl)ethylphosphonic acid (**3b**)*: Yield: 1.95 g (87%); white solid: mp 204–207 °C; IR (KBr): 3297–2302 (OH), 1801, 1603, 1545, 1119 (P=O), 1050 (P–OH), 965 cm^{-1}; ^1H NMR (600 MHz, H_2O/D_2O, 9/1, NaOH): δ = 1.75–1.80 (m, 2H, CH_2P), 2.01 (s, 3H, CH_3), 3.83–3.87 (m, 2H, CH_2N), 4.92 (s, 1H, CH); ^{13}C NMR (151 MHz, H_2O/D_2O, 9/1, NaOH): δ = 13.3 (CH_3), 36.6 (d, $^1J_{PC}$ = 124.4 Hz, CH_2P), 41.2 (CH_2N), 86.0 (CH_{arom}), 149.2 (C-3), 162.1 (C-5); ^{31}P NMR (243 MHz, H_2O/D_2O, 9/1, NaOH): δ = 18.01; Anal. Calcd for $C_6H_{11}N_2O_4P{\cdot}H_2O$: C, 32.15; H, 5.85. Found: C, 32.15; H, 5.81.

16. *2-[5-Hydroxy-3-(trifluoromethyl)pyrazol-1-yl]ethylphosphonic acid (**3c**)*: A solution of **1** (1.40 g, 10.0 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in H_2O (8 mL) was refluxed for 1 min. Next, ethyl 3-oxo-4,4,4-trifluorobutyrate (1.84 g 10.0 mmol) was added and the mixture refluxed for 3 h. The mixture was concentrated to ~4 mL and extracted with Et_2O (3 × 5 mL). The aqueous phase was acidified with HCl (aq) solution (4 mol/L, 5 mL) and evaporated. The residue was crystallised from H_2O to give the product as colourless crystals (0.82 g, 32%); mp 192–196 °C; IR (KBr): 3420–2340 (OH), 1571, 1505, 1418, 1180, 1127 (P=O), 1022 (P–OH), 992 cm^{-1}; ^1H NMR (600 MHz, H_2O/D_2O, 9/1, NaOH): δ = 2.17–2.23 (m, 2H, CH_2P), 4.19–4.24 (m, 2H,CH_2N), 5.88 (s, 1H, CH); ^{13}C NMR (151 MHz, H_2O/D_2O, 9/1, NaOH): δ = 27.3 (d, $^1J_{PC}$ = 133.4 Hz, CH_2P), 41.6 (CH_2N), 86.2 (CH), 120.9 (q, $^1J_{FC}$ = 268.1 Hz, CF_3), 140.6 (q, $^2J_{FC}$ = 37.9, C-3), 153.0 (C-5); ^{31}P NMR (243 MHz, H_2O/D_2O, 9/1, NaOH): δ = 23.33; Anal. Calcd for $C_6H_8N_2O_4P{\cdot}0.27\ H_2O$: C, 27.20; H, 3.25. Found: C, 27.20; H, 3.29.

17. *2-(5-Amino-3-phenylpyrazol-1-yl)ethylphosphonic acid (**3d**)*: A mixture of **1** (0.70 g, 5.0 mmol) and benzoylacetonitrile (0.73 g, 5.0 mmol) in MeOH/H_2O (3/1, 40 mL) was refluxed and stirred for 18 h. The clear solution thus obtained was concentrated to 10 mL. The crude product was separated by filtration, washed with H_2O (2 × 5 mL), acetone (2 × 5 mL) and Et_2O (5 mL) and crystallised from H_2O to give the pure product as colourless crystals (0.90 g, 67%); mp 116–118 °C; IR (KBr): 3335–2362 (OH, NH), 1648, 1598, 1561, 1508, 1473, 1238 (P=O), 1135, 1050, 1028, 923 (P–OH) cm^{-1}; ^1H NMR (600 MHz, H_2O/D_2O, 9/1, NaOH): δ = 1.87–1.93 (m, 2H, CH_2P), 4.12–4.16 (m, 2H, CH_2N), 5.97 (s, 1H, CH), 7.35–7.68 (m, 5H, CH_{arom}); ^{13}C NMR (151 MHz, H_2O/D_2O, 9/1, NaOH): δ = 30.1 (d, $^1J_{PC}$ = 123.6 Hz, CH_2P), 44.1 (CH_2N), 88.5 (C-4), 125.4 (CH_{arom}), 128.4 (CH_{arom}), 129.1 (CH_{arom}), 132.6 (C_{arom}), 147.3 (C-5), 150.8 (C-3); ^{31}P NMR (243 MHz, H_2O/D_2O, 9/1, NaOH): δ = 16.66; Anal. Calcd for $C_{11}H_{14}NO_3P$: C, 49.44; H, 5.28; N, 15.72. Found: C, 49.12; H, 5.24; N, 15.45.

18. *Phthalazine derivatives **4a**,**b**; general procedure*: To a soln of **1** (1.40 g, 10.0 mmol) and Na_2CO_3 (1.06 g, 10.0 mmol) in H_2O (10 mL), was added the dicarbonyl compound (10.0 mmol) and the mixture was refluxed for 15 min. The resulting clear solution was cooled and acidified with concd HCl (aq) soln (3 mL). The precipitate was filtered, washed with H_2O (2 × 5 mL) and acetone (5 mL) and dried (100 °C, 6 h).

    *2-(4-Hydroxy-1-oxophthalazin-2-yl)ethylphosphonic acid (**4a**)*: Yield: 1.95 g (56%); colorless crystals: mp 249–253 °C; IR (KBr): 3423–2275 (OH), 1618, 1568, 1548, 1497, 1452, 1254 (P=O), 1074, 1021 (P–OH), 980 cm^{-1}; ^1H NMR (600 MHz, D_2O/NaOD): δ = 1.91–1.96 (m, 2H, CH_2P), 4.13–4.17 (m, 2H, CH_2N), 7.76–7.84 (m, 2H, H-6, H-7), 8.01–8.13 (m, 2H, H-5, H-8); ^{13}C NMR (151 MHz, D_2O/NaOD): δ = 28.9 (d, $^1J_{PC}$ = 124.4 Hz, CH_2P), 48.2 (CH_2N), 125.5 (C-5), 125.7 (C-8), 128.4 (C-4a), 129.4 (C-8a), 131.6 (C-6), 132.9 (C-7), 161.5 (C-4); ^{31}P NMR (243 MHz, D_2O/NaOD): δ = 17.65; Anal. Calcd for $C_{10}H_{11}N_2O_5P$: C, 44.46; H, 4.10. Found: C, 44.35; H, 4.25.

    *2-(4-Hydroxy-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl)ethylphosphonic acid (**4b**)*: Yield: 2.47 g (90%); colorless crystals: mp 255–258 °C; IR (KBr): 3440–2259 (OH), 1551, 1485, 1452, 1311, 1274, 1140 (P=O), 993 (P–OH) cm^{-1}; ^1H NMR (600 MHz, H_2O/D_2O, 9/1, NaOH): δ = 1.61–1.66 (m, 4H, $2CH_2$), 1.97–2.02 (m, 2H, CH_2P), 2.35–2.38 (m, 4H, $2CH_2$), 4.08–4.12 (m, 2H, CH_2N); ^{13}C NMR (151 MHz, H_2O/D_2O, 9/1, NaOH): δ = 20.4 (C-6 or C-7), 20.6 (C-7 or C-6), 23.5 (C-5 or C-8), 23.6 (C-8 or C-5), 27.6 (d, $^1J_{PC}$ = 128.7 Hz, CH_2P), 46.9 (CH_2N), 138.0 (C-4a or C-8a), 138.7 (C-8a or C-4a), 157.9 (C-4), 159.3 (C-3); ^{31}P NMR (243 MHz, H_2O/D_2O, 9/1, NaOH): δ = 20.13; Anal. Calcd for $C_{10}H_{15}N_2O_5P$: C, 43.80; H, 5.51. Found: C, 43.79; H, 5.42.