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LETTERS TO THE EDITOR

Novel Approach to Synthesis of β-Hydroxyphosphonic Acids

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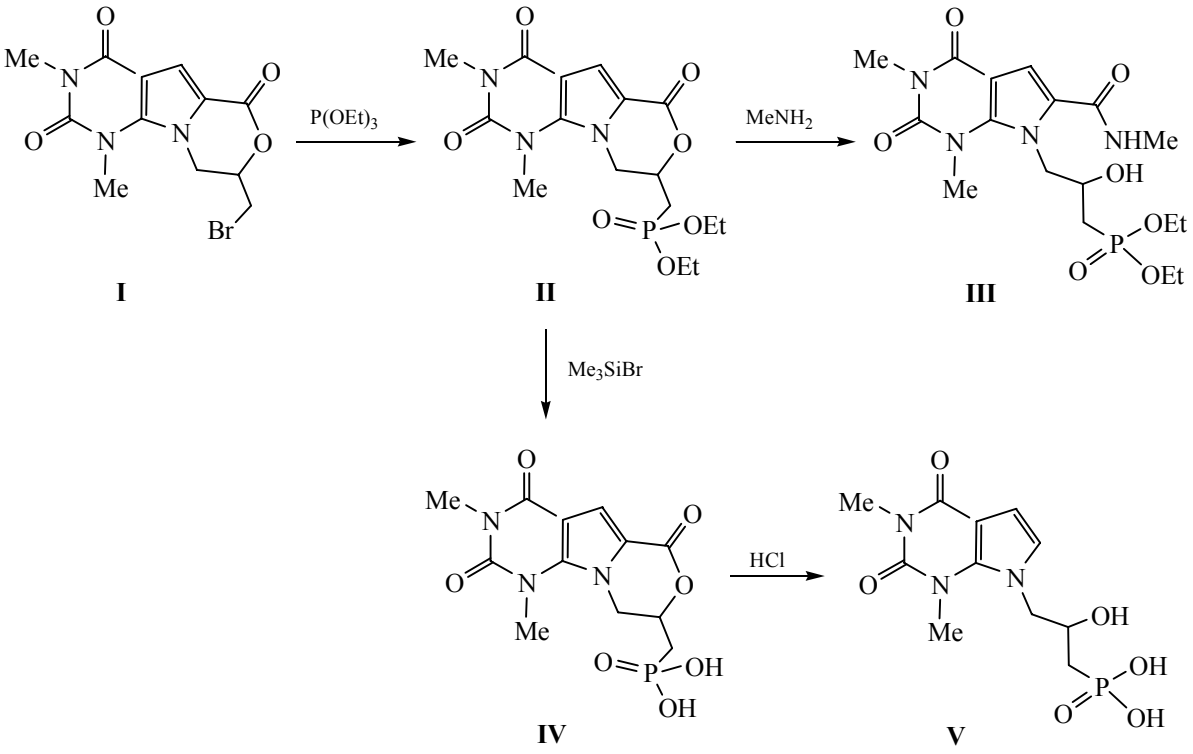
Synthesis of phosphonate of the acyclic nucleoside analogs has been recently targeted at preparation of novel compounds revealing high antiviral activity [1, 2]. β-Hydroxyphosphonates, structural analogues of Adefovir (PMEA), have attracted particular attention. Their preparation is based on alkylation of the heterocyclic ring at nitrogen atom [3–5]. Here, we propose a new approach to synthesize phosphorylated derivatives of pyrrolo[2,3-*d*]pyrimidine. 8-Bromomethylpyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine **I** [6] was used as the initial compound. The Arbuzov reaction of **I** with triethylphosphite gave diethyl [(1,3-dimethyl-2*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]-oxazin-8-yl)methyl]phosphonate **II**. Reaction of the lactone **II** with methylamine resulted in lactone ring opening to form amide of pyrrolo[2,3-*d*]-pyrimidine-6-carboxylic acid **III** containing 2-hydroxy-3-diethyl-phosphonopropyl fragment at C^7 of the heterocyclic ring. β-Hydroxypropylphosphonic acid **V** was obtained via sequential treating of compound **II** with trimethylbromosilane and diluted hydrochloric acid. The reaction occurred through the lactone ring opening accompanied by decarboxylation.



Structures of the so prepared compounds were elucidated by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and IR spectroscopy as well as by elemental analysis.

Diethyl {(1,3-dimethyl-2,4,6-trioxo-1,3,4,6,8,9-hexahydro-2*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-yl)methyl}phosphonate (II). A mixture of 2.0 g of compound **I** and 6 mL of triethyl phosphite was refluxed during 24 h and then cooled to 20–25°C. The formed precipitate was filtered off and washed with ethanol. Yield 1.7 g (74%), mp 231–233°C (C_2H_5OH). ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.30–1.36 m (6H, 2$\underline{CH_3}CH_2O$), 2.16–2.27 m (1H) and 2.41–2.51 m (1H, CH_2P), 3.38 s (3H, NCH_3), 3.78 s (3H, NCH_3), 4.10–4.18 m (4H, 2$CH_3\underline{CH_2}O$), 4.46–4.51 m (1H) and 4.90–4.98 m (2H, NCH_2, CH), 7.56 s (1H, CH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 16.4 ($OCH_2\underline{C}H_3$), 28.5 (NCH_3), 29.4 d (CH_2P, $^1J_{CP}$ 145.0 Hz), 31.9 (NCH_3), 47.3 (C^9), 62.9 ($O\underline{C}H_2CH_3$), 72.0 (C^8), 103.2 (C^{4a}), 115.7 (C^5), 116.8 (C^{5a}), 138.8 (C^{10a}), 151.5 (2-C=O), 157.1 (6-C=O), 158.0 (4-C=O). ^{31}P NMR spectrum (DMSO-d_6): δ_P 26.4 ppm. Found, %: C 48.15; H 5.61; N 10.59; P 7.82. $C_{16}H_{22}N_3O_7P$. Calculated, %: C 48.12; H 5.55; N 10.52; P 7.76.

Diethyl [3-(1,3-dimethyl-6-methylaminocarbonyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-hydroxypropyl]phosphonate (III). Solution of 0.15 g of methylamine in 5 mL of methanol was added to suspension of 0.5 g of compound **II** in 5 mL of methanol. The mixture was refluxed during 2 h, then cooled to 20–25°C and incubated during 12 h at that temperature. The formed precipitate was filtered off and washed with methanol. Yield 0.2 g (38%), mp 182–184°C (C_2H_5OH). IR spectrum, ν, cm^{-1}: 1643 (C=O), 1706 (C=O), 3317 br (NH), 3387 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 1.20–1.25 m (6H, 2$\underline{CH_3}CH_2O$), 1.88–1.96 m (2H, CH_2P), 2.72 d (3H, NH$\underline{CH_3}$, $^3J_{HH}$ 4.0 Hz), 3.24 s (3H, NCH_3), 3.74 s (3H, NCH_3), 3.93–4.04 m (5H, 2$CH_3\underline{CH_2}O$, CH), 4.61–4.66 m (1H) and 4.88–4.95 m (1H, NCH_2), 5.33 d (1H, OH, $^3J_{HH}$ 6.0 Hz), 7.13 s (1H, CH), 8.29 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 16.7 ($OCH_2\underline{C}H_3$), 26.3 (NCH_3), 28.4 (NCH_3), 31.2 (CH_2P, $^1J_{CP}$ 115.0 Hz), 33.4 ($NHCH_3$), 51.8 (NCH_2), 61.5 ($O\underline{C}H_2CH_3$), 66.4 (CH), 100.3(C^{4a}), 109.2 (C^5), 126.3 (C^6), 142.1 (C^{7a}), 152.2 (2-C=O), 158.7 (6-C=O), 161.8 (4-C=O). ^{31}P NMR spectrum (DMSO-d_6): δ_P 29.3 ppm. Found, %: C 47.58; H 6.28; N 12.94; P 7.32. $C_{17}H_{27}N_4O_7P$. Calculated, %: C 47.44; H 6.32; N 13.02; P 7.20.

[(1,3-Dimethyl-2,4,6-trioxo-1,3,4,6,8,9-hexahydro-2*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-yl)methyl]phosphonic acid (IV). 1.82 mL of trimethylsilyl bromide was added to suspension of 0.92 g of compound **II** in 10 mL of acetonitrile. The mixture was incubated at 20–25°C during 12 h. The solvent was then removed in vacuum, and the residue was treated with 10 mL of water. The precipitate was filtered off and washed with water. Yield 0.67 g (85%), mp 245–247°C (decomp., water). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 2.12–2.16 m (2H, CH_2P), 3.25 s (3H, NCH_3), 3.69 s (3H, NCH_3), 4.54 d. d (1H, $^3J_{HH}$ 13.2, $^3J_{HH}$ 9.2 Hz) and 4.90–4.94 m (2H, NCH_2, CH), 7.30 s (1H, CH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.5 (NCH_3), 31.0 d (CH_2P, $^1J_{CP}$ 129.0 Hz), 32.0 (NCH_3), 47.8 (C^9), 73.6 (C^8), 102.4 (C^{4a}), 113.5 (C^5), 117.5 (C^{5a}), 139.5 (C^{10a}), 151.6 (2-C=O), 158.3 (6-C=O), 158.4 (4-C=O). ^{31}P NMR spectrum (DMSO-d_6): δ_P 19.7 ppm. Found, %: C 41.93; H 4.15; N 12.29; P 9.07. $C_{12}H_{14}N_3O_7P$. Calculated, %: C 41.99; H 4.11; N 12.24; P 9.02.

3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxypropylphosphonic acid (V). Mixture of 0.5 g of compound **IV** and 5 mL of aqueous HCl (1 : 1) was refluxed during 6 h, then cooled to 20–25°C and incubated during 12 h at that temperature. The formed precipitate was filtered off and washed with water. Yield 0.2 g (43%), mp. 233–235°C (decomp., water). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 1.80–1.84 m (2H, CH_2P), 3.23 s (3H, NCH_3), 3.73 s (3H, NCH_3), 3.99–4.05 m (1H, CH), 4.22 d d (1H, $^3J_{HH}$ 15.0, $^3J_{HH}$ 7.0 Hz) and 4.47 d d (1H, NCH_2, $^3J_{HH}$ 3.0, $^3J_{HH}$ 15.0 Hz), 6.39 d (1H, CH, $^3J_{HH}$ 3.5 Hz), 6.74 d (1H, CH, $^3J_{HH}$ 3.5 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.3 (NCH_3), 32.6 (NCH_3), 34.6 d (CH_2P, $^1J_{CP}$ 135.0 Hz), 54.2 (NCH_2), 67.3 (CH), 100.9 (C^{4a}), 103.4 (C^5), 123.9 (C^6), 138.8 (C^{7a}), 151.8 (2-C=O), 158.8 (4-C=O). ^{31}P NMR spectrum (DMSO-d_6): δ_P 22.2 ppm. Found, %: C 41.55; H 5.12; N 13.16; P 9.82. $C_{11}H_{16}N_3O_6P$. Calculated, %: C 41.65; H 5.08; N 13.25; P 9.76.

NMR spectra of solutions in DMSO-d_6 were registered with Bruker Avance DRX 500 spectrometer [^{1}H, 500 MHz (**V**); ^{31}P, 202 MHz; ^{13}C, 125 MHz] and

with Varian Unity plus 400 spectrometer [^{1}H, 400 MHz (**II**–**IV**)]. TMS and 85% H_3PO_4 were used as internal and external references, respectively. IR spectra of KBr pellets were recorded with Bruker Vertex 70 FTIR instrument.

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