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Formation of phostonic acids during the reduction of azidonucleosidephosphonic acids†

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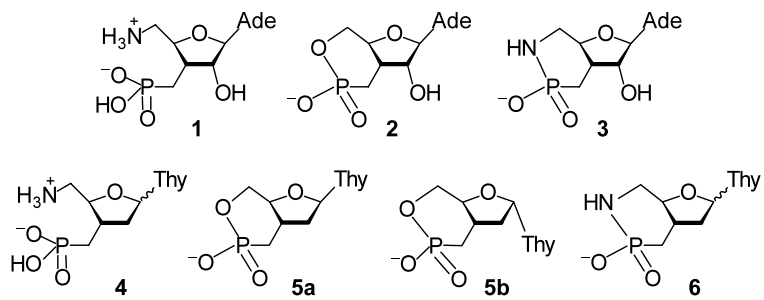
Abstract—Reduction of 5′-azido-3′,5′-dideoxy-3′-(phosphorylmethyl)nucleosides, either with H_2/Pd/C or with dithiothreitol, leads to cyclic phosphonate esters (phostonic acids) in addition to the desired 5′-amino compounds. The phostonic acids are obtained as the main products when a 20-fold excess of dithiothreitol is used.

Phosphonic acid analogs of nucleotides are interesting objects of biological studies because the stability of their P–C bonds makes them resistant towards the action of phosphatases.[1] Phostonic acids, cyclic esters of phosphonic acids, are also known from various classes of biomolecules.[2] Some time ago, we reported the synthesis of 2′,3′-dideoxy-3′-(phosphonomethyl)-nucleosides which are phosphonate analogs of 2′-deoxy-3′-nucleotides.[3] In connection with this work and with the studies by Moffatt et al.[1] we became interested in the synthesis and properties of 5′-amino-3′,5′-dideoxy-3′-(phosphonomethyl)-nucleosides such as **1** and of the corresponding 2′,3′,5′-trideoxy nucleosides such as **4** (Scheme 1).

The preparation of **1** and **4** from their azido precursors was accompanied by the formation of title compounds **2** and **5a**/**5b**, respectively, as major sideproducts. In fact, these phostonic acids can be made the main products when a large excess of the reducing agent dithiothreitol is used. Cyclization of **1** or **4** with water-soluble carbodiimide yields the novel *c*AMP analog **3** and the *c*dTMP analog **6**, respectively, which contain the 3′-CH_2 and 5′-NH groups in the newly formed six-membered ring. The present communication describes the synthetic pathways to **1**–**3** and to **4**–**6**.

Moffatt's compound **7**[1] was treated with *p*-toluenesulfonyl chloride in dry pyridine (0°C, 5 h) to give tosylate **8**, which was reacted with lithium azide in dimethylformamide to furnish good yields (>85%) of azide **9** (Scheme 2). Acetolysis of the 1,2-*O*-isopropylidene group of **9** gave crystalline 1,2-di(*O*-acetyl)-5-azido-3,5-dideoxy-3-(diethoxyphosphorylmethyl)-β-D-ribofuranose (**10**). Compound **10** was converted to **11**



Scheme 1.

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† In memoriam Dr. Ludger Witte (1948–2001).

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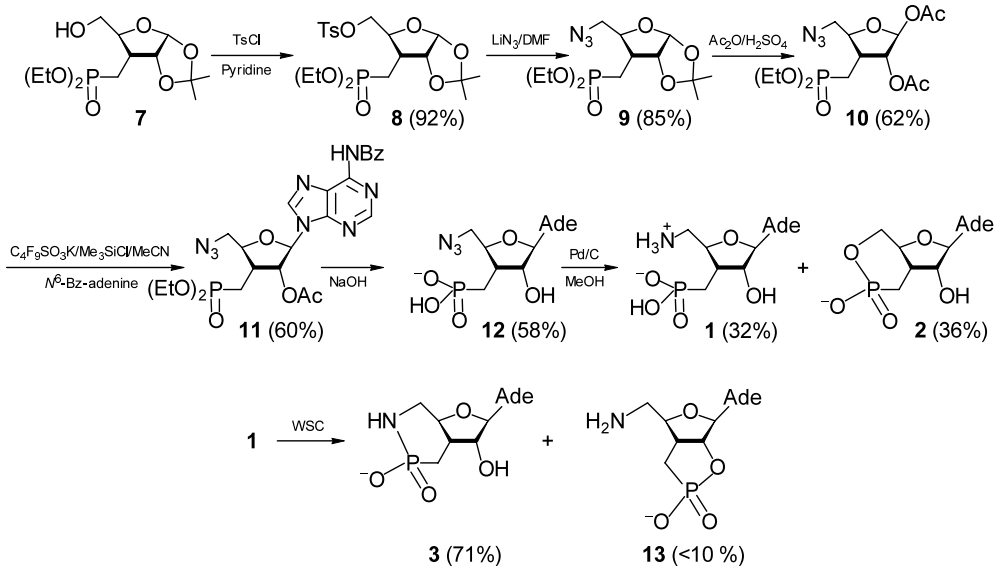
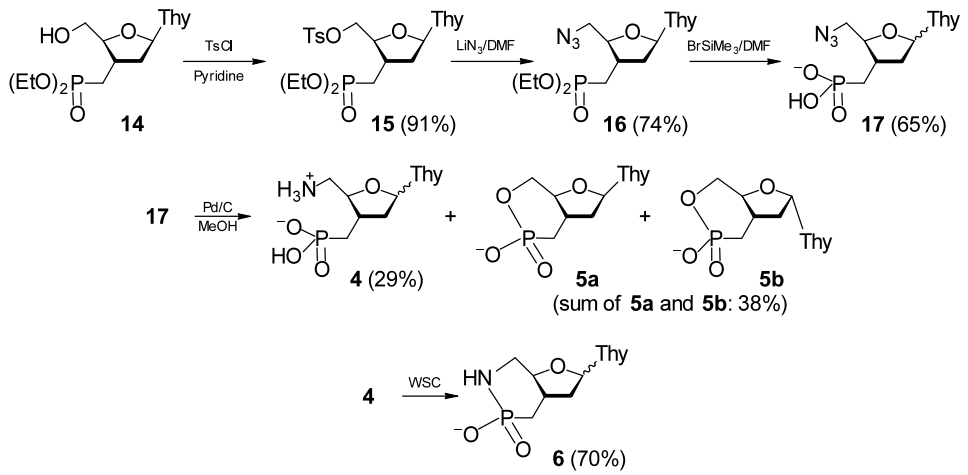


Scheme 2.

(60% yield) with N^6-benzoyladenine using the one-pot procedure of Vorbrüggen with potassium perfluorobutanesulfonate and chlorotrimethylsilane in acetonitrile.[4,5] Ester **11** was hydrolyzed with 1N NaOH to give the sodium salt of phosphonic acid **12**, which was purified by ion-exchange chromatography on DEAE-Sephadex (HCO_3^- form) and eluted with a gradient of water/triethylammonium bicarbonate buffer. Subsequent hydrogenation of **12** with H_2 in methanol in the presence of Pd/charcoal gave the expected aminophosphonic acid **1** and, surprisingly, phostonic acid **2**, a *c*AMP analog that had been prepared in a different way by Moffatt in 10% yield.[6] Aminoacid **1** was cyclized with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide ('WSC', 20-fold excess) to give the *c*AMP analog **3**, in which the 3′- and 5′-oxygens are replaced by carbon and nitrogen, respectively. The ^{31}P NMR spectrum of the crude product, however, also contained a foreign signal at $\delta = +43$ ppm characteristic of a five-membered ring, which indicated[7] that some cyclization involving the 2′-OH group had also occurred to give phostonic acid **13**.

In order to test whether the formation of a phostonic acid during catalytic reduction is specific to adenosine derivatives, hydrogenation of the thymine analog **17** was also investigated (Scheme 3). Tosylation of compound **14**, previously described by us,[3] gave **15**, which was converted to azide **16**. Alkaline hydrolysis of the ester groups of **16** was not successful due to the lack of neighboring group assistance by the 2′-OH group. Hence, **16** was transesterified[8] with bromotrimethylsilane in the presence of 2,4,6-trimethylpyridine and hydrolyzed with water to give azido acid **17**. However, this reaction was accompanied by some epimerization of C-1′ and the product contained ca. 30% of the α-anomer. After ion-exchange chromatography the anomeric mixture of **17** was obtained in 65% yield. The subsequent hydrogenation in methanol was monitored by thin-layer chromatography which showed that aminoacid **4** was the main product, accompanied by ca. 38% of phostonic acids **5a**/**5b**. After ion-exchange chromatography the latter mixture was separated into the anomers by HPLC on a C8 column. Cyclization of **4**



Scheme 3.

with WSC gave a 70% yield of cyclic 3′,5′-aminophosphonate **6**.

A recent paper by Reardon et al.[9] on the reduction of 3′-azido-3′-deoxythymidine (AZT) and of AZT-5′-monophosphate with dithiothreitol (DTT), which gave, among other products, 9% of D-*threo*-thymidine 3′,5′-cyclic monophosphate, led us to apply DTT for the reduction of our above azidophosphonates. Both in the reduction of **12** and in that of **17** at neutral pH with a 20-fold excess of DTT we obtained the phostonic acids **2** and **5**, respectively, as the main products (over 50% yield). The reduction of 5′-azido-5′-deoxyadenosine 3′-phosphate did not give *c*AMP, neither catalytically nor with DTT. The formation of phostonic acids **2** and **5** as opposed to *c*AMP could be favored by the conformation of the P–C moiety at C-3′ (*gauche–anti*), which differs from that of a 3′-phosphate group.[3] The leaving group is possibly the partially hydrogenated azido group (–NH–N=NH) as suggested by Reardon et al.[9]

The structures of all new compounds were verified by the usual spectroscopic techniques, in particular by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Characteristic features of the cyclized compounds **2** and **3** are the spin–spin coupling between ^{31}P and the protons at C-5′ in **3** (not visible in **2** because of the complexity of the spectrum due to the coincidence of the H-4′ and H-5′$_b$ chemical shifts) and the coupling between ^{31}P and C-5′ in **2** and **3**. In the comparison of the ^{13}C NMR spectra of **2** and **3** (phostonic acid versus phostamic acid) the replacement of O by NH is indicated by the shielding of C-5′ ($\delta = 44.5$ in **3** versus 67.8 in **2**), by the shielding of the protons at C-5′ ($\delta = 4.5$–4.1 in **3** versus 3.47 and 3.16 in **2**), and by the large decrease of $^{1}J_{PC}$ (109.4 Hz in **3** versus 122.5 Hz in **2**) due to the lower electronegativity of nitrogen relative to oxygen as a ligand at the phosphorus center. By way of illustration the NMR data of **1**–**3** are given below.

1: ^{1}H NMR [400 MHz, D_2O, pD = 8.6, δ(HOD) = 4.80)]: $\delta = 8.37$, 8.29 (both s; H-2, H-8), 6.18 (d; H-1′), 4.95 (dd; H-2′), 4.42 (ddd; H-4′), 3.59 (dd; H-5′$_a$), 3.44 (dd; H-5′$_b$), 2.76 (m; H-3′), 1.90 (ddd; PCH_a), 1.73 (ddd; PCH_b); $J(1',2') = 1.9$, $J(2',3') = 5.9$, $J(3',P) = 8.7$, $J(3',4') = 9.8$, $J(3',PCH_a) = 8.8$, $J(3',PCH_b) = 5.8$, $J(PCH_a,PCH_b) = (-)14.9$, $J(PCH_a,P) = (-)16.7$, $J(PCH_b,P) = (-)17.4$, $J(4',5'_a) = 3.3$, $J(4',5'_b) = 6.4$, $J(5'_a,5'_b) = (-)13.8$ Hz. ^{13}C NMR [75 MHz, D_2O, pD = 8.6, δ(int. Dioxan) = 67.4]: 156.0 (C_q; C-6), 153.1 (CH; C-2), 148.9 (C_q; C-4), 140.5 (CH; C-8), 119.4 (C_q; C-5), 91.0 (CH; C-1′), 82.5 (CH; d, $J_{PC} = 14.3$ Hz; C-4′), 77.5 (CH; d, $J_{PC} = 5.2$ Hz; C-2′), 41.9 (CH_2; C-5′), 41.8 (CH; d, $J_{PC} = 3.1$ Hz; C-3′), 25.1 (CH_2; d, $J_{PC} = 127.9$ Hz; PCH_2). ^{31}P NMR [162 MHz, D_2O, ext. H_3PO_4]: $\delta = 19.1$. HRMS (ESI): $m/z =$ 343.0935 $(M-H)^-$, calcd for $C_{11}H_{16}N_6O_5P$ 343.0920.

2: ^{1}H NMR [400 MHz, D_2O, δ(HOD) = 4.80)]: $\delta = 8.20$, 8.19 (both s; H-2, H-8), 6.14 (d; H-1′), 4.58 (br. d; H-2′), 4.47–4.36 (m; H-5′$_a$), 4.21–4.12 (m; H-4′ and H-5′$_b$), 2.61 (br. m; H-3′), 2.01 (ddd; PCH_a), 1.82 (dt; PCH_b); $J(1',2') = 1.3$, $J(3',PCH_a) = 3.2$, $J(3',PCH_b) = 13.5$, $J(PCH_a,PCH_b) = (-)13.9$, $J(PCH_a,P) = (-)17.0$, $J(PCH_b,P) = (-)15.9$. ^{13}C NMR [101 MHz, D_2O, δ(int. Dioxan) = 67.4]: 156.3 (C_q; C-6), 153.5 (CH; C-2), 148.9 (C_q; C-4), 140.1 (CH; C-8), 119.5 (C_q; C-5), 93.3 (CH; C-1′), 78.2 (CH; d, $J_{PC} = 4.4$ Hz; C-4′), 76.9 (CH; d, $J_{PC} = 14.7$ Hz; C-2′), 67.8 (CH_2; d, $J_{PC} = 5.8$ Hz; C-5′), 45.0 (CH; d, $J_{PC} = 5.5$ Hz; C-3′), 23.3 (CH_2; d, $J_{PC} =$ 122.5 Hz; PCH_2). ^{31}P NMR [162 MHz, D_2O, ext. H_3PO_4]: $\delta = 21.9$. HRMS (ESI): $m/z = 326.0689$ $(M-H)^-$, calcd for $C_{11}H_{13}N_5O_5P$ 326.0655.

3: ^{1}H NMR [300 MHz, D_2O, δ(HOD) = 4.80)]: $\delta = 8.26$, 8.25 (both s; H-2, H-8), 6.14 (d; H-1′), 4.57 (d; H-2′), 4.02 (td; H-4′), 3.47 (ddd; H-5′$_a$), 3.16 (td; H-5′$_b$), 2.55 (br. m, $\Sigma J = 37.8$ Hz; H-3′), 1.96 (ddd; PCH_a), 1.77 ('q'; PCH_b); $J(1',2') = 1.5$, $J(2',3') = 4.4$, $J(3',4') = 11.2$, $J(3',PCH_a) = 3.1$, $J(3',PCH_b) = 13.4$, $J(PCH_a,PCH_b) = (-)13.7$, $J(PCH_a,P) = (-)18.3$, $J(PCH_b,P) = (-)13.4$, $J(4',5'_a) = 4.4$, $J(4',5'_b) = 11.0$, $J(5'_a,5'_b) = (-)12.5$, $J(5'_a,P) = 23.0$, $J(5'_b,P) = 1.6$ Hz. ^{13}C NMR [75 MHz, D_2O, δ(int. Dioxan) = 67.4]: 155.9 (C_q; C-6), 153.1 (CH; C-2), 148.6 (C_q; C-4), 139.7 (CH; C-8), 119.2 (C_q; C-5), 92.1 (CH; C-1′), 80.2 (CH; d, $J_{PC} = 5.2$ Hz; C-4′), 77.0 (CH; d, $J_{PC} = 13.5$ Hz; C-2′), 44.9 (CH; d, $J_{PC} = 4.5$ Hz; C-3′), 44.4 (CH_2; d, $J_{PC} = 2.0$ Hz; C-5′), 25.6 (CH_2; d, $J_{PC} =$ 109.4 Hz; PCH_2). ^{31}P NMR [121 MHz, D_2O, ext. H_3PO_4]: $\delta = 23.7$. HRMS (ESI): $m/z = 325.0821$ $(M-H)^-$, calcd for $C_{11}H_{14}N_6O_4P$ 325.0814.

References

1. Albrecht, H. P.; Jones, G. H.; Moffatt, J. G. *Tetrahedron* **1984**, *40*, 79–85.
2. Hanessian, S.; Rogel, O. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2441–2446.
3. Morr, M.; Ernst, L.; Schomburg, D. *Liebigs Ann. Chem.* **1991**, 615–631.
4. Vorbrüggen, H.; Bennua, B. *Tetrahedron Lett.* **1978**, 1339–1342.
5. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255.
6. Jones, G. H.; Albrecht, H. P.; Damodaran, N. P.; Moffatt, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 5510–5511.
7. McClard, R. W.; Witte, J. F. *Bioorg. Chem.* **1990**, *18*, 165–178.
8. Valentijn, A. R. P. M.; van den Berg, O.; van der Marel, G. A.; Cohen, L. H.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 2099–2108.
9. Reardon, J. E.; Crouch, R. C.; St. John-Williams, L. *J. Biol. Chem.* **1994**, *269*, 15999–16008.