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A Novel Type of Nucleoside Analogue with Penta-Coordinated Phosphorus

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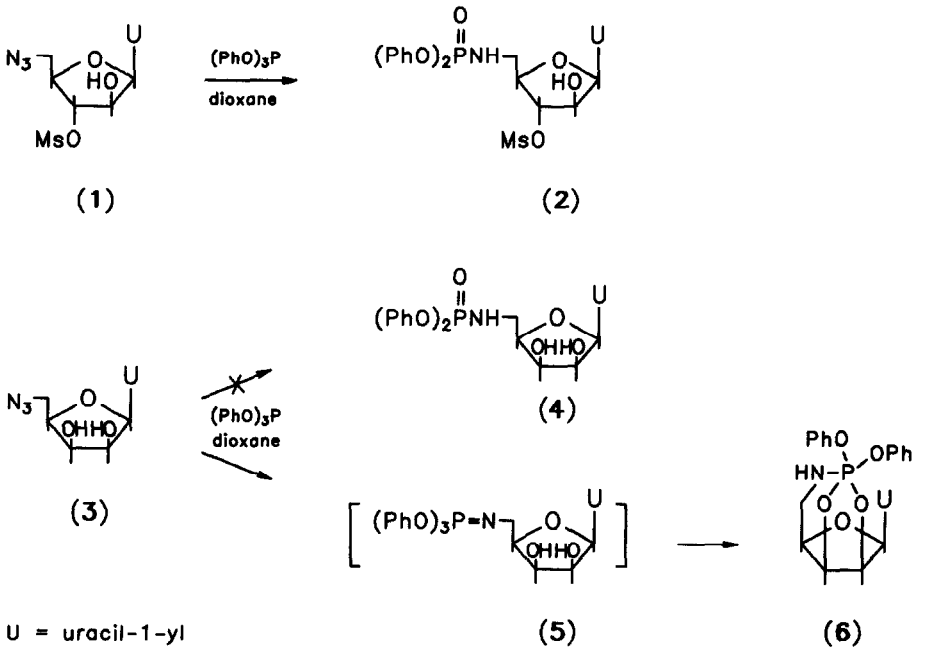
Abstract: The reaction of 1-(5-azido-5-deoxy-β-D-lyxofuranosyl)uracil(**3**) with triphenyl phosphite afforded a cyclic phosphorane (**6**) rather than the anticipated 5'-phosphoramido lyxoside (**4**). The structure of this nucleoside analogue with penta-coordinated phosphorus is based on ^{1}H, ^{13}C and ^{31}P NMR spectra.

In the tremendous efforts directed toward the discovery of efficient anti-HIV agents it was found that certain inactive nucleoside analogues could be activated by simple chemical phosphorylation[1]. Another approach to improve the therapeutic potential of the nucleoside analogues is directed to the design of phosphate-modified derivatives which may penetrate the cell membrane and liberate the bio-active nucleotides intracellularly[2]. It was found that certain phosphoramidate nucleoside analogues are potent inhibitors of viral proliferation[3]. On the other hand, the phosphoramidate derivatives of chemotherapeutic nucleoside analogues are also of interest regarding the enhanced enzymatic and chemical stability of the P-N bond[4]. In this respect we became interested in nucleotide analogues having 3'- or 5'-oxygen replaced by nitrogen atom suitable for preparation of the respective phosphoramidates[5]. In extension of our previous work we planed to prepare the 5'-phosphoramidates starting from 1-(5-azido--5-deoxy-3-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1**)[5] and 1-(5-azido-5-deoxy-β-lyxofuranosyl)uracil (**3**)[5] by using the described coupling of azides and triphenyl phosphite and the conversion of the initially formed 5'-phosphite imines into the phosphoramidates by a mechanism similar to the Michaelis-Arbuzov reaction[6]. In the present communication we report on these studies and the unexpected formation of the first nucleoside analogue (**6**) having penta-coordinated phosphorus.

While the reaction of (**1**) (R_f=0.30,CH_2Cl_2:MeOH=10:1) with triphenyl phosphite in dioxane at 100°C gave the expected 5'-phosphoramido product (**2**) (R_f=0.26) in good yield (87%), the reaction of *lyxo*-nucleoside (**3**) (R_f=0.18) in the same reaction conditions gave the product of surprisingly high t.l.c. mobility (R_f=0.58). The expected structure (**4**) of the product was ruled out on the basis of the ^{1}H, ^{13}C and ^{31}P NMR spectra[7]. The ^{1}H NMR spectrum shows a two signals as doublet-doublet-doublet centered at δ_H 4.89 and δ_H 4.52 ppm. The assignment of these signals to the H-3' and H-2' is readily made with

aid of COSY spectrum . The appearance of coupling between the phosphorus and 2'- and 3'-sugar ring protons ($^3J_{P,H\text{-}3'}$=24.9 Hz, $^3J_{P,H\text{-}2'}$=15.4 Hz) and absence of OH signals suggested C2'-O-P and C3'-O-P connections in the molecule. This together with the observed small coupling constant between H-1' and H-2' ($J_{1',2'}$=2.4 Hz) are in accordance with the phosphorus containing cyclic system, *cis*-attached on C-2' and C-3' atoms of the sugar moiety. The assignment of C-atom signals in ^{13}C NMR spectrum is supported by heteronuclear ^{1}H-^{13}C experiment. The resonances attributable to the C-2' and C-3' exhibited downfield chemical shifts (cca 3 ppm) relative to dihydroxy compound (**3**)[5], in accordance with phosphorylation deshielding effect[8]. The signals of C-atoms of the two phenyl groups indicated their nonequivalence arising from their attachment on the rigid structure. The broadband ^{1}H decoupled ^{31}P NMR spectrum shows a singlet signal at δ -54.3 ppm, characteristic of penta-coordinated phosphorus[9], whereas in coupled spectrum this signal appears as multiplet with ^{1}H-^{31}P coupling constants of $^3J_{P,H\text{-}3'}$=24.2 Hz and $^3J_{P,H\text{-}2'}$=15.2 Hz. The tricyclic structure (**6**) with penta-coordinated phosphorus would provide a logical explanation for the observed spectroscopic data. The reaction is believed to proceed *via* initially formed phosphite imine (**5**) and its subsequent reaction with sterically conveniently oriented *lyxo*-hydroxyl groups (Scheme 1).

Scheme 1

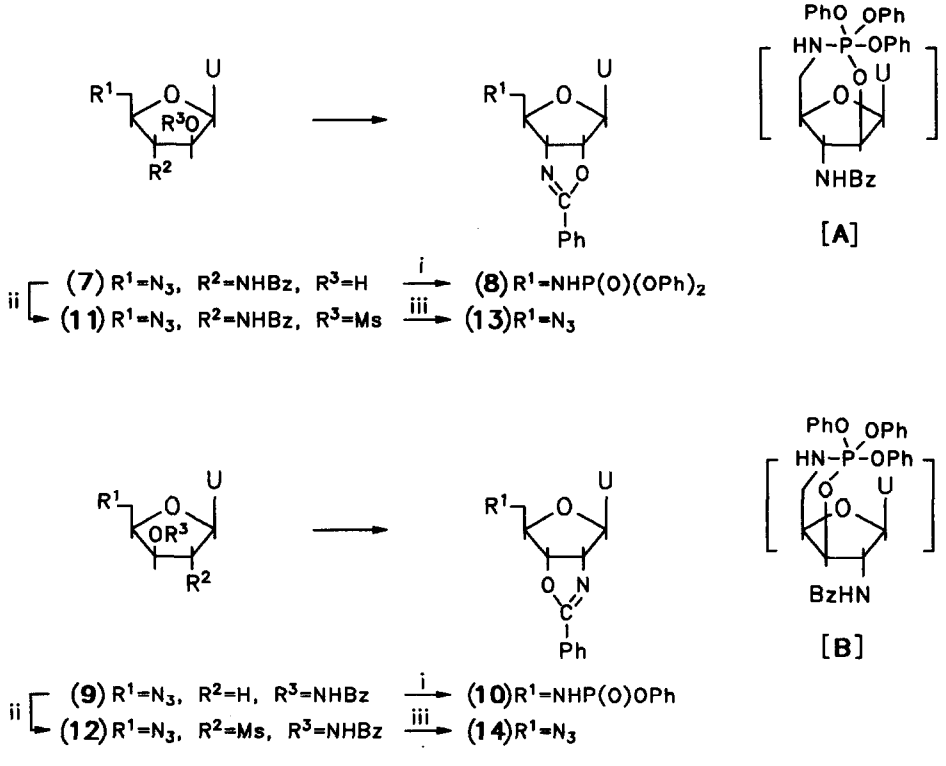


To the best of our knowledge no example of the corresponding system in the nucleoside field has been reported to date, although penta-coordinate phosphorus compounds are known since the pioneering

work of Ramirez on the preparation of stable phosphoranes[10].

In the light of the found conversion of (3) into (6) we did not exclude the possibility of formation of the cyclic 1,3-oxazaphosphoranes [A] and [B] with participation of 2'- or 3'-hydroxyl group in (7) and (9), respectively, although in the reaction of (1) with triphenyl phosphite we were not able to detect the formation of such product. It is well known that the solvolysis of esters of phosphoric acid is profoundly enhanced by neighboring nucleophilic group[11]. Based on this fact we assumed that the presence of suitable nucleophilic group, such as benzamido group[12] in (7) and (9) should result in intramolecular nucleophilic ring opening of [A] or [B], if formed, giving the oxazolines (8) and (10), respectively. The structures of oxazolines (8) and (10) obtained in the reactions of (7) and (9) with triphenyl phosphite were compared with (13) and (14) prepared independently by heating of mesylates (11) and (12) in DMF (Scheme 2).

Scheme 2



Reagents and conditions: i, $(PhO)_3P$ / dioxane; ii, MsCl / py; iii, DMF, Δ

The selected ^1H NMR data for oxazolines (8), (10), (13) and (14) presented in Table I, clearly show the structurally similar neighborhood of H-1', H-2', and H-3' protons in (8) and (13) as well as in (10) and (14).

In conclusion, we report on the preparation of a novel type of cyclic nucleoside analogue (6) the containing penta-coordinated phosphorus, and present the indirect evidence for the formation of the

Table I Selected chemical shifts (in ppm) and coupling constants (in Hz) of oxazolines (**8**), (**10**), (**13**) and (**14**) in DMSO-d_6.

Compound	H-1'	H-2'	H-3'	$^3J_{1',2'}$	$^3J_{2',3'}$	$^3J_{3',4'}$
(**8**)	5.84	5.46	4.76	2.95	8.80	4.94
(**10**)	5.76	5.09	5.24	2.45	8.45	4.45
(**13**)	5.98	5.59	4.80	3.00	8.85	4.85
(**14**)	5.88	5.16	5.26	2.65	8.80	4.60

1,3-oxazaphosphorane intermediates [**A**] and [**B**] in the conversions of (**7**) and (**9**) into oxazoline derivatives (**8**) and (**10**), respectively. Further studies on this type of cyclic phosphorane are currently in progress.

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REFERENCES AND NOTES

1. McGuigan, C.; Kinchington, D.; Wang, M.F.; Nicholls, S.R.; Nickson, C.; Galpin, S.; Jeffries, D.J.; O'Connor, T.J. *FEBS Lett.* **1993**, 322, 249.
2. Farrow, S.N.; Jones, A.S.; Kumar, A.; Walker, R.T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1990**, 33, 1400.
3. McGuigan, C.; Devine, K.G.; O'Connor, T.J.; Kinchington, D. *Antiviral Res.* **1991**, 15, 255.
4. Hunston, R.N.; Jehangir, M.; Jones, A.S.; Walker, R.T. *Tetrahedron* **1980**, 36, 2337.
5. Katalenić, D.; Škarić, V. *J. Chem. Soc. Perkin Trans. I* **1992**, 1065.
6. a) Freist, W.; Schattka, K.; Cramer, F.; Jastorff, B. *Chem. Ber.* **1972**, 105, 991.
   b) Kvita, V.; Baschang, G. *Helv. Chim. Acta* **1972**, 55, 2683.
7. Spectra were recorded in DMSO-d_6 on Varian Gemini 300 spectrometer operating at 300 (^{1}H), 75.45 (^{13}C) or 121.44 (^{31}P) MHz, respectively, using standard Gemini software-package. The spectra were referenced to residual DMSO-d_6 signal (2.51 (^{1}H) or 39.6 (^{13}C) ppm, respectively). Chemical shift of ^{31}P spectrum is negative when was upfield from external standard of 80% aqueous H_3PO_4.
8. Mantsch, H.H.; Smith, J.C.P. *Biochem. Biophys. Res. Commun.* **1972**, 46, 808.
9. Ramirez, F.; Ugi, I.; Lin, F.; Pfohl, S.; Hoffman, P.; Marquarding, D. *Tetrahedron* **1974**, 30, 371.
10. Ramirez, F. *Accounts Chem. Res.* **1968**, 1, 168.
11. Zioudrou, C.; Schmir, G.L. *J. Amer. Chem. Soc.* **1963**, 85, 3258.
12. It well known in carbohydrate chemistry that the unionized benzamido group *O*-participates in the intramolecular nucleophilic substitution at the vicinal center carrying *trans*-positioned leaving group: Baker, B.R.; Schaub, R.E. *J. Org. Chem.* **1954**, 19, 646.

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