A One-pot Synthesis of Cyclic Pyrido[1,2-*a*]quinoxaline Phosphate, a New Molecule of Biological Importance from a Quinoxaline Derivative of Sugar

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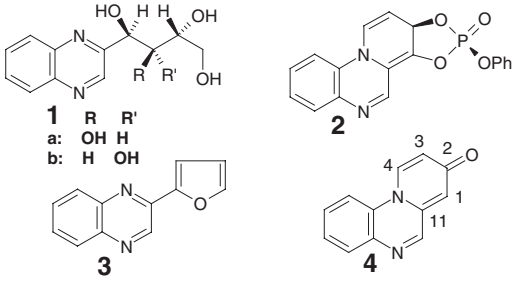
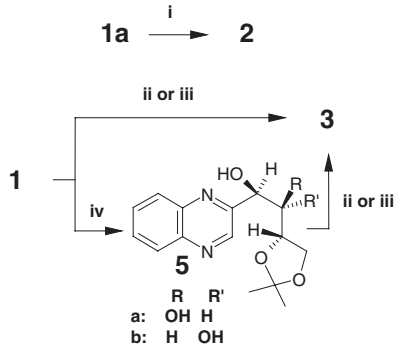
A five membered cyclic pyrido[1,2-*a*]quinoxaline phosphate has been first synthesized in one step in a good yield by phosphorylation of the quinoxaline derivative of sugar **1a** with $(PhO)P(O)Cl_2$. Phosphorylation of the tetrols (**1a** and **1b**) and the diol acetals with other phosphorylating agents, however, affords a dehydration product 2-(2-furyl)quinoxaline.

Quinoxaline and their derivatives have found use in antitumor antibiotics,[1a-c] potent bacteriocides,[1d] molecular recognition research,[1e] colorimetric sensors[1f] and consequently they have become the subject of intense research for their biochemical significance.[1g,h] 2-(D-arabino-Tetrahydroxybutyl)quinoxaline **1a** is a long known molecule[2] and has been used as a pteridine analogue[3] for synthetic studies on the molybdenum cofactor.[4] Synthetic phosphoric esters of 6-hydroxyquinoxaline and ester derivatives of 2-hydroxyquinoxaline have also found use in insecticidal preparations and anthelmintics.[1g] Cyclic phosphates are important constituents and are present in a large number of biologically important molecules.[5] However, no report has been made for the synthesis of a cyclic phosphate onto a quinoxaline system. We wish to report a simple and an efficient synthesis of such a new heterocyclic phosphate triester where the phosphate moiety is present in a five membered ring which is attached to the pyrido[1,2-*a*]quinoxaline system.



In continuation[5] of our work, we have investigated the possibility of phosphorylation reaction with the tetrol **1a** to obtain an α-hydroxyphosphate where the phosphate would be present in a six membered ring under a variety of reaction conditions. Thus when the tetrol **1a** is subjected to reaction with $(PhO)P(O)Cl_2$, 16-phenoxy-13*H*-15,17-dioxa-6,9-diaza-16-phosphacyclopenta[a]phenanthrene16-oxide **2**, an unprecedented five membered cyclic phosphate, was obtained in a good yield. This one step procedure thus efficiently creates both six and five membered fused heterocyclic rings onto a quinoxaline system resulting a novel cyclic pyrido[1,2-*a*]quinoxaline phosphate by ring closure followed by dehydration of the tetrol **1a** with $(PhO)P(O)Cl_2$ (Scheme 1).

However, treatment of **1a**–**b** with $(EtO)_3P(O)$ or $POCl_3$, $(PhO)P(O)Cl_2$, $(p\text{-}O_2N\text{-}C_6H_4O)P(O)Cl_2$, 2-phenyl-bis-triazolo-

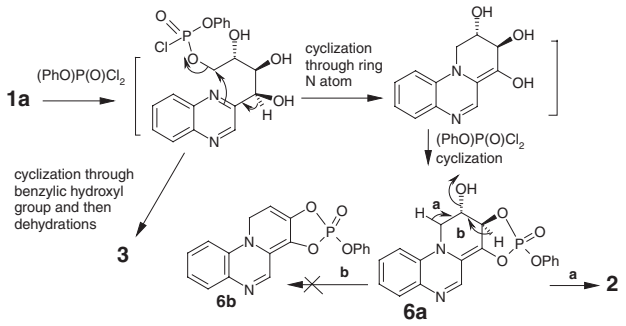


Scheme 1. Reagent and conditions: i. $(PhO)P(O)Cl_2$ neat, rt, **5h**. ii. $(EtO)_3P(O)$ neat or $POCl_3/(PhO)P(O)Cl_2/(p\text{-}O_2N\text{-}C_6H_4O)P(O)Cl_2$/2-phenyl-bis-triazoloyl phosphate/tris(1,2,4-triazoloyl) phosphate in dioxane/CH_3CN and Et_3N or in pyridine, rt, 4-6 h. iii. H^+, rt, 4-6 h. iv. dry acetone, conc. H_2SO_4, rt, 12 h.

yl phosphate[6a] and tris(1,2,4-triazoloyl) phosphate[6b] with various solvents containing Et_3N such as dioxane, CH_3CN and also in pyridine resulted a product which is solely found to be 2-(2-furyl)quinoxaline **3**. Acid treatment (concentrated H_2SO_4, concentrated HCl, HCl in absolute alcohol as well as AcOH and H_3PO_4) of **1a**–**b** also led to the formation of **3**, previously which was however wrongly assigned as glucazidone **4**.[7] We also first report here the complete spectral proof (^1H, ^{13}C, MS, and IR data) in favour of the structure **3**.

In order to rationalize the role of these phosphorylating agents, we have tested the phosphorylation reactions on diol acetals[8] (**5a** and **5b**) under the similar conditions and we isolated **3** as the sole product in each case in good yields. From the above findings (Scheme 1), we have reasoned that instead of phosphorylation, triethyl phosphate, triazolides and other phosphorus acid chlorides that are used, favoured the side chain dehydration of the tetrols (**1a** and **1b**) and their diol acetals (**5a** and **5b**) resulting the formation of furan ring attached to quinoxaline **3**. The five membered pyrido[1,2-*a*]quinoxaline phosphate **2** was synthesized in one step from the tetrol **1a** by reaction with neat $(PhO)P(O)Cl_2$ in a good yield (85%).

The structure **2** is established[9] on the basis of detailed spectral analysis (FTIR, ^1H, ^{13}C (normal & DEPT), ^{31}P and MS) which is also supported from the following plausible mechanism (Scheme 2). Phenylphosphorodichloridate phosphorylates the tetrol **1a** while initially attacking the terminal alcohol[6a] which follows cyclization to 6a, through pyrazine ring nitrogen or cyclization followed by dehydrations to **3** through benzylic hydroxyl group. Dehydration of **6a** follows the stereoelectronically more favourable path **a** than path **b** (to **6b**) which, may give **2** exclusively.



Scheme 2. Plausible mechanism for the formation of **2**.

The ^{1}H NMR spectrum however shows a *cis* coupling constant ($J = 6.9$ Hz) for the vicinal olefin protons which is consistent with the structure **2**. Further, DEPT-135 experiment has also suggested that the double bonds are present between C_{11}-C_1 and C_3-C_4 atoms. The ESI MS shows an intense peak at m/z 353.9 (MH^+). Thus, careful analysis of all the spectral data confirms the structure **2** for the product.

X-ray crystallographic studies[10a] of several five membered cyclic phosphate esters have established that alkoxy group on phosphorus is directed away from the ring. The large negative (−30.12 ppm) ^{31}P chemical shift value of **2** and those found in other five membered cyclic phosphate esters[10b,c] suggest that the compound **2** exists as a single conformer at room temperature.

In conclusion, the first one-pot synthesis of a cyclic pyrido[1,2-*a*]quinoxaline phosphate **2**, a new heterocyclic phosphate triester of biological significance is reported by a simple and an efficient method. Interestingly, on reaction with acids and other phosphorylating agents, the tetrols and the diol acetals formed **3** as the sole product.

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8 Compounds **1** and **5** are prepared by the similar procedure reported in Refs. 2b and 3a respectively. Selected physical data for compound **5a**: mp 129-131 °C [lit[3a] 145-146 °C]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.0 (s, 1H, quinoxalin-2-yl), 8.16–8.14 (m, 2H), 8.07-8.05 (m, 2H), 5.24 (dd, 1H, $J = 2.0$, 2.0 Hz), 4.30–4.25 (m, 2H, OH and c_4-H), 4.19 (m, 1H), 4.09 (m, 2H), 3.07 (brs, OH), 1.46 and 1.38 (2 × s, 6H, 2 × CH_3). MS (FD): m/z (%): 290 (M^+, 100), 275 (50), 189 (40). The spectroscopic data for compound **5b** is in accord with the structure given. For a recent preparation of **1a** and **1b** see: S. P. Goswami and A. K. Adak, *Tetrahedron Lett.*, **43**, 8371 (2002).

9 A suspension of the tetrol **1a** (1.0 g, 3.98 mmol) and (PhO)P(O)Cl_2 (1.0 mL) was stirred under nitrogen atmosphere at ice bath (0–5 °C) for 1 h and then at rt for 4 h. Water (40 mL) was then added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed well with brine, dried ($MgSO_4$) followed by evaporation with rotary evaporator afforded a brown solid which was purified on silica gel (100-200 mesh) column chromatography eluting with pertoleum ether : CH_2Cl_2 (3:2) gave **2** (0.88 g, 85%) as a brown crystalline solid. mp 84–86 °C. UV ($CHCl_3$) λ_{max} (log ε): 369 (4.09) and 284 (4.23) nm. FT-IR (KBr): 3137, 2925, 1612, 1588, 1552, 1497, 1297, 1189, 1083, 1058, 1002, 963, 917, 775, 758, 688, 594 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.23 (s, 1H, quinoxalin-2-yl), 8.09 (d, 1H, $J = 8.8$ Hz), 8.05 (d, 1H, $J = 8.8$ Hz), 7.75-7.70 (m, 2H), 7.67 (d, 1H, $J = 6.9$ Hz), 7.35-7.30 (m, 4H), 7.24 (d, 1H, $J = 8.4$ Hz), 7.20 (t, 1H, $J = 7.3$ Hz), 6.61 (qt, 1H, $J = 1.7$, 1.7, 1.7 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): 152.00, 150.87 (d, $J = 7.3$ Hz), 145.49, 144.25, 142.48, 142.45, 141.68, 130.84, 130.25 (d, $J = 0.8$ Hz), 129.72, 129.61, 126.0 (d, $J = 1.2$ Hz), 120.54, 120.50, 112.90, 112.23. ^{1}H decoupled ^{31}P NMR ($CDCl_3$, 202 MHz): −30.12. MS (ESI): m/z (%): 353.9 (MH^+, 20), 349.0 (100), 327 (30), 196 (25). Calcd. for $C_{18}H_{13}N_2O_4P$: required C, 61.37; H, 3.72; N, 7.95%. Found C, 61.35; H, 3.78; N, 7.99%. Selected physical data for compound **3**: Yield: (80%); off-white solid; mp 76–78 °C. FT-IR (KBr): 3136, 3116, 1736, 1612, 1552, 1497, 1224, 1169, 1082, 916, 657, 594, 589 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.25 (s, 1H, quinoxalin-2-yl), 8.11 (d, 1H, $J = 8.3$ Hz), 8.07 (d, 1H, $J = 8.3$ Hz), 7.77-7.72 (m, 2H), 7.69 (d, 1H, $J = 7.3$ Hz), 7.33 (d, 1H, $J = 3.4$ Hz), 6.64 (qt, 1H, $J = 1.6$, 1.7, 1.7 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): 151.97, 145.55, 144.23, 142.47, 142.43, 141.67, 130.93, 129.77, 129.61 (d, $J = 1.2$ Hz), 129.53, 112.88, 112.19. MS (ESI): m/z (%): 196 (M^+, 100), 168 (30). Calcd. for $C_{12}H_8N_2O$: required C, 73.46; H, 4.11; N, 14.28%. Found C, 73.48; H, 4.15; N, 14.30%.

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