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SIMPLE SYNTHESIS OF 9-(5-DEOXY-β-D-ERYTHRO-PENT-4-ENOFURANOSYL)ADENINE FROM ADENOSINE BY SELENOXIDE FRAGMENTATION

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5'-Se-(2-Nitrophenyl)-5'-selenoadenosine (3) was selectively synthesized by the reaction of adenosine with 2-nitrophenylselenocyanate and tri-n-butylphosphine. The selenide 3 was oxidized by treatment with excess hydrogen peroxide to the corresponding selenoxide (4), which readily undergo syn elimination under mild conditions to give the corresponding 9-(5-deoxy-β-D-erythro-pent-4-enofuranosyl)-adenine (5) in good yield.

The nucleoside antibiotic angustmycin A[1] and nucleocidin[2] are known to have antibacterial, antitumor, and antitrypanosomal activity. 9-(5-Deoxy-β-D-erythro-pent-4-enofuranosyl)adenine (5) is a key intermediate for the synthesis of antibiotics related to angustmycin A and nucleocidin. The synthesis of such unsaturated nucleosides was utilized an elimination of leaving group ($4\text{-MeC}_6\text{H}_4\text{SO}_3$, MeSO_3, Br, or I) from the C(5') carbon.[3] It became evident in time that these synthetic methods occurred a number of problems, among which were N(3)-C(5') cyclonucleosides formation during substitution or elimination reactions or difficulties in the selective removal of acid label blocking group.[4] In this communication, we report a simple preparative method for 5 from adenosine through the reaction of adenosine with 2-nitrophenylselenocyanate and tri-n-butylphosphine, followed by oxidation and syn elimination of the resulting 5'-Se-(2-nitrophenyl)-5'-selenoadenosine (3).[5]

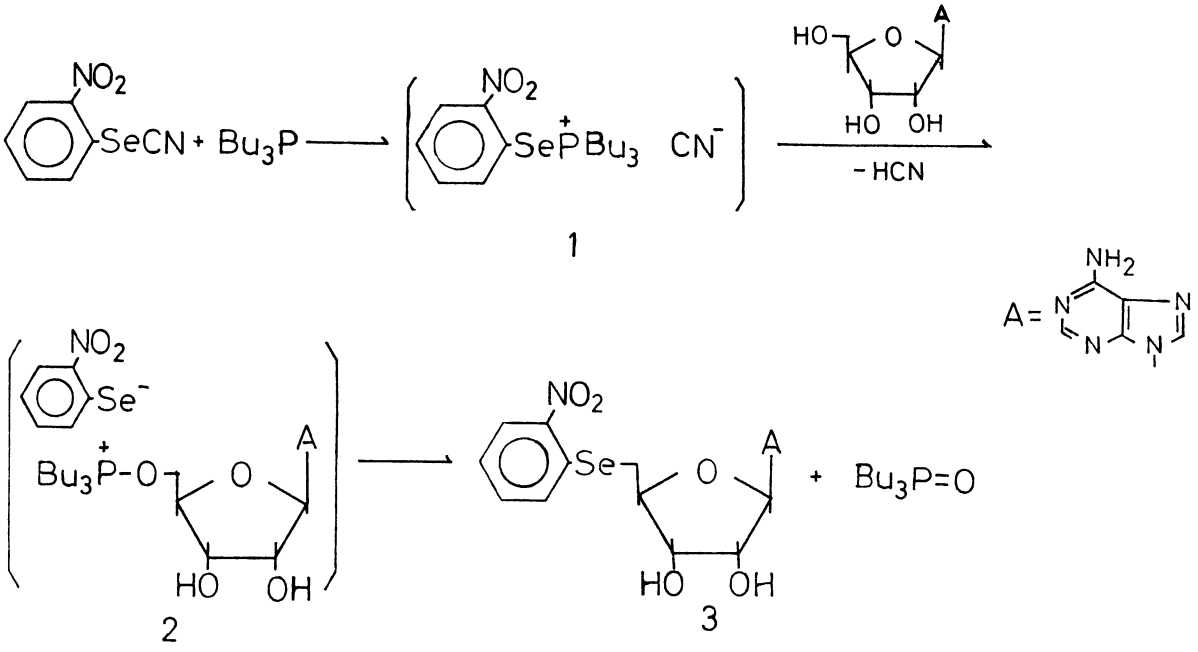
We first examined the selective synthesis of 3 by the reaction of adenosine with 2-nitrophenylselenocyanate[6] and tri-n-butylphosphine: To a suspension of adenosine (534 mg, 2.0 mmol) in dry pyridine (20 ml) was added 2-nitrophenylselenocyanate (1.36 g, 6.0 mmol) and tri-n-butylphosphine (1.21 g, 6.0 mmol) at room temperature. The suspension became clear after 1 h because of consumption of slightly soluble adenosine in the progress of the reaction. After stirring 23 h, the reaction mixture was quenched with water and the solution was evaporated to dryness. The residue was chromatographed on a column of silica gel. The compound 3 was isolated in 874 mg (94%) by eltuting the coulmn with a stepwise gradient of methanol (0-20%) in methylene chloride: mp 127-129°C; UV λmax (MeOH) 256 nm (ε=28,100), λmin(MeOH) 235 nm; NMR (DMSO-d_6) δ 3.66 (m, 2H, H-5' and 5"), 4.15-4.41 (m, 2H, H-3' and H-2'), 4.89 (q, 1H, H-4'), 5.49 (d, 1H,

C_2'-OH), 5.65 (d, 1H, C_3'-OH), 5.98 (d, 1H, $J_{1',2'}$=6 Hz, H-1'), 7.31 (s, 2H, NH_2), 7.42-8.38 (m, 4H, Ar), 8.18 (s, 1H, H-2 or H-8), 8.35 (s, 1H, H-2 or H-8), (5.49, 5.64, and 7.31 disappeared by addition of D_2O); Calcd for $C_{16}H_{16}N_6O_5Se \cdot H_2O$: C, 40.94; H, 3.86; N, 17.79%. Found: C, 40.55; H, 3.63; N, 17.79%. In this reaction, when di(2-nitrophenyl) diselenide was used in place of 2-nitrophenylselenocyanate, the yield of 3 decreased markedly (see Table 1). Furthermore, tri-n-butylphosphine afforded 3 from adenosine in higher yield than triphenylphosphine.

Table 1. Synthesis of 5'-Se-(2-nitrophenyl)-5'-selenoadenosine (3).

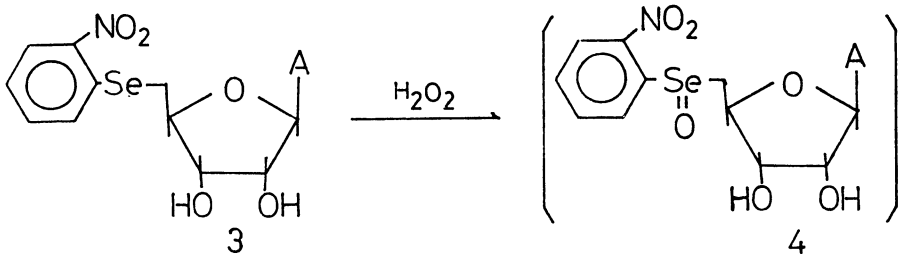
adenosine (mmol)	2-O_2NPhSeCN (mmol)	Bu_3P (mmol)	pyridine (ml)	time (hr)	yield (%)
0.3	0.3	0.3	3	48	9
0.3	0.3	0.3	DMF 3	48	10
0.3	0.45	0.45	3	48	62
0.3	0.6	0.6	3	48	65
2.0	6.0	6.0	20	24	94
0.3	0.9	Ph_3P 0.9	3	48	12
0.3	(2-O_2NPhSe)$_2$ 0.9	0.9	3	48	15

The reaction seems to proceed through a selenophosphonium salt (1) which reacts with adenosine providing an oxaphosphonium salt (2). Reaction of the selenium anion with the oxaphosphonium species in 2 is likely to provide the corresponding 5'-Se-(2-nitrophenyl)-5'-selenoadenosine (3).



Next, the synthesis of 5 from 3 was examined. The compound 3 (902 mg, 2.0 mmol) was oxidized with 30% hydrogen peroxide (1.72 ml, 20 mmol) in THF (50 ml) at room temperature for 2 h to the stable selenoxide 4 [7]. The solution was evaporated to dryness and the residue was treated with triethylamine (2.81 ml, 2.0 mmol) in pyridine (10 ml) at 50°C for 12 h. The solution was evaporated to dryness and the residue was dissolved in methanol-water (7:3 v/v) (10 ml) and applied to a column of Dowex 1-X2 (OH^- form, 200-400 mesh). Elution of the column with methanol-water (7:3 v/v) gave 448 mg (90%) of 5 which was proved to be homogeneous by tlc and NMR: mp 184-185°C (lit.[4] mp 185-186°C); Rf=0.65 (CH_2Cl_2-MeOH, 7:3 v/v); UV λmax 259 nm (ε=14,300); NMR (DMSO-d_6-D_2O) δ 4.21 (d, 1H, H-5'a), 4.35 (br d, 1H, H-5'b), 4.97 (m, 2H, H-2' and H-3'), 6.35 (d, 1H, $J_{1',2'}$=4.8Hz, H-1'), 8.34 (s, 1H, H-2 or H-8), 8.46 (s, 1H, H-2 or H-8); Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10%. Found: C, 48.41; H, 4.39; N, 28.05%.

On the other hand, heating the solution of 4 in pyridine at 100°C recovered 4 unchanged. Triethylamine effectively promotes syn elimination of the selenoxide group and hydrogen at 4' position.



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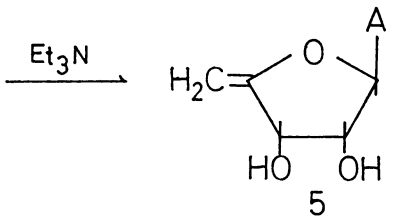

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In conclusion, it was noted that 9-(5-deoxy-β-D-erythro-pent-4-enofuranosyl)adenine (5) was prepared in good yield by two steps without using the protecting groups on hydroxyl groups of sugar moiety and amino group of nucleoside base throughout the synthetic steps. Further studies on the synthesis of an exocyclic double bond in other nucleosides are now in progress.

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7) The compound 4 was isolated in 91% yield: mp 154-156°C; UV λmax(MeOH) 260 nm; NMR (DMSO-d_6-D_2O) δ 3.35 (d, 1H, H-5'a), 3.75 (d, 1H, H-5'b), 4.21-4.42 (m, 2H, H-3' and H-2'), 4.87 (dd, 1H, H-4'), 5.96 (d, 1H, $J_{1',2'}$=5.8 Hz, H-1'), 7.45-8.31 (m, 4H, Ar), 8.12 (s, 1H, H-2 or H-8), 8.36 (s, 1H, H-2 or H-8); Calcd for $C_{16}H_{17}O_6N_6Se.H_2O$: C, 39.60; H, 3.73; N, 23.08%. Found: C, 39.49; H, 3.83; N, 23.17%.

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