

SYNTHESIS OF Se⁸,2'-CYCLO-8-SELENO-9-β-D-ARABINOFURANOSYLADENINE:
A NOVEL PURINE CYCLONUCLEOSIDE WITH A SELENIUM-BRIDGE

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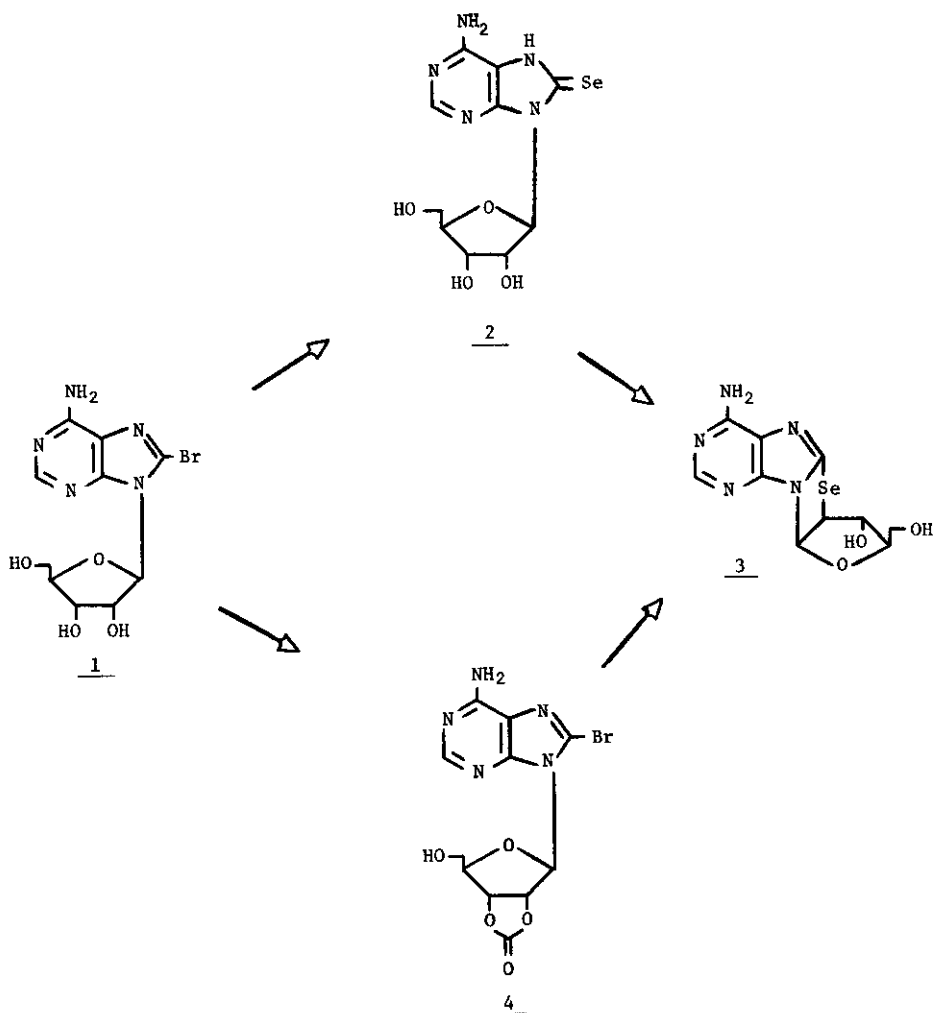
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Abstract: The synthesis of 8-selenoadenosine (2) and Se⁸,2'-cyclo-8-seleno-8-β-D-arabinofuranosyladenine (3) are described. This synthesis of 3 involved the first use of 2-acetoxyisobutyryl chloride for the preparation of a purine cyclonucleoside.

Purine cyclonucleosides possessing either O-cyclo or S-cyclo linkages have proven to be quite versatile intermediates.^{1,2} Sulfur cyclonucleosides have been of particular interest since desulfurization provides a facile method for the conversion of purine ribonucleosides into the corresponding purine deoxyribonucleosides. Using this technique, S⁸,2'-cyclo-8-mercapto-9-β-D-arabinofuranosyladenine and S⁸,3'-cyclo-8-mercapto-9-β-D-arabinofuranosyladenine were desulfurized with Raney-nickel to afford 2'-deoxyadenosine^{3a} and 3'-deoxyadenosine (cordycepin),^{3b} respectively. We have been involved in the synthesis of selenonucleosides as potential anticancer agents⁴ and on the use of selenium *vs* sulfur in our synthesis program. Recently, we reported the synthesis of the first selenium-bridged nucleoside, Se²,2'-cyclo-2-selenocytidine.⁵ This successful synthesis prompted us to investigate the synthesis of the purine cyclonucleoside, Se⁸,2'-cyclo-8-seleno-9-β-D-arabinofuranosyladenine (3).

We chose to investigate the use of 2-acetoxyisobutyryl chloride for our initial approach toward the synthesis of the desired Se⁸,2'-cyclo-8-seleno-9-β-D-arabinofuranosyladenine (3), since similar type reactions in the pyrimidine series occurred under mild reaction conditions. This method involved a synthesis of the previously unreported 8-selenoadenosine (2) and the subsequent reaction of 2 with 2-acetoxyisobutyryl chloride to effect the cyclonucleoside formation. 2-Acetoxyisobutyryl chloride has been used extensively in pyrimidine cyclonucleoside formation,⁶ however, to our knowledge, it has not been applied in the preparation of purine cyclonucleosides. The synthesis of 8-selenoadenosine (2) was accomplished by treatment of 8-bromoadenosine (1) (1 g, 2.9 mmole) with selenourea (600 mg, 4.9 mmole) in absolute ethanol which afforded a yellow product in 60% yield, mp 125-127°; uv [λ_{max} in nm ($\epsilon \times 10^{-3}$)] H₂O, 310 (29.2). 8-Selenoadenosine (2) (347 mg, 1 mmole) was reacted with 2-acetoxyisobutyryl chloride (4 mmole) in acetonitrile at room temperature for 5 hr, during this time the solution became colorless. The reaction was

filtered, 100 ml of diethyl ether added to the filtrate, and the resulting precipitate was collected by filtration and washed with ether. This solid, without further purification, was then treated with 10 ml of 0.18 N methanolic hydrogen chloride at room temperature for 14 hr. Evaporation to dryness and recrystallization of the resulting residue from water furnished Se⁸,2'-cyclo-



8-seleno-β-D-arabinofuranosyladenine (3), (54%): mp 212° (dec); uv [$\lambda_{\max}$ in nm ($\epsilon \times 10^{-3}$)] H₂O, 277 (21.9); pH = 1, 283 (21.4), pH = 11, 277 (21.8); ¹H-NMR (Me₂SO-d₆) δ 6.46 (1H, H-1', d, $J_{1',2'} = 6$ Hz), δ 8.17 (1H, H-2, s). Cyclonucleoside formation was demonstrated by: 1) a direct comparison of the uv spectra of 3 with 8-methylselenoadenosine⁷ and S⁸,2'-cyclo-8-mercapto-β-D-arabinofuranosyladenine;⁸ 2) the expected hypsochromic wavelength shift in the uv spectra between 3 and 2; and 3) the similarity of the pmr spectra of 3 with that of O⁸,2'-oxocycloadenosine and S⁸,2'-thiocycloadenosine.⁸ Therefore, this constitutes the first synthesis of a selenium-bridged

purine cyclonucleoside. Further, we have, in addition to the synthesis of 3, demonstrated that 2-acetoxyisobutyryl chloride may be used in the synthesis of purine cyclonucleosides. This procedure, which takes place under very mild conditions, should also prove applicable to the synthesis of $O^8,2'$ -cyclo- as well as $S^8,2'$ -cyclopurine nucleosides.

To further substantiate the constitution of the product, we prepared 3 by a second method of synthesis which involved a procedure similar to that reported by Ogilvie and Slotin⁹ for the synthesis of $S^8,2'$ -cyclo-8-mercapto-9- β -D-arabinofuranosyladenine. 8-Bromoadenosine-2',3'-carbonate (4) (1.63 g, 4.4 mmole) was suspended in *n*-butanol (100 ml). Nitrogen gas was passed through the solution for 0.5 hr, selenourea (0.6 g, 4.8 mmole) was then added and the mixture was heated at reflux temperature for 7 hr while being protected from light. During the reaction, the solution turned yellow, then colorless. The reaction mixture was cooled to room temperature, and the solvent removed *in vacuo*. The resulting residue was suspended in ethanol (50 ml) at room temperature and filtered. The filtrate was reduced in volume to 10 ml, and then 10 ml of water was added. This furnished a product (40%) which proved to be identical (tlc, uv, pmr and mp) to that obtained by the first procedure.¹⁰

We have found¹¹ that reactions such as deseleniation or nucleophilic displacement of exocyclic alkylseleno ethers in purine nucleosides generally occur under milder conditions (room temperature and reaction times less than 10 min) than reaction conditions required for the corresponding sulfur analogs. Studies involving the chemical reactivity of this novel purine selenium-bridged cyclonucleoside are under active investigation in our laboratory.

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REFERENCES

1. M. Ikehara, H. Tada, K. Muneyama and M. Kaneko, *J. Am. Chem. Soc.*, 1966, **88**, 3165.
2. M. Ikehara and N. Kaneko, *Tetrahedron*, 1970, **26**, 4251.
3. a) M. Ikehara and H. Tada, *Chem. Pharm. Bull.*, 1967, **15**, 94; b) M. Ikehara and H. Tada, 'Synthetic Procedures in Nucleic Acids,' Vol. 1, eds. by Zorbach and Tipson, Wiley Interscience, 1968, p. 188.
4. L. B. Townsend and G. H. Milne, *Ann. NY Acad. Sci.*, 1975, **255**, 91.
5. D. S. Wise and L. B. Townsend, *J.C.S. Chem. Comm.*, 1979, 271.
6. For a review see: J. G. Moffatt, 'Nucleoside Analogues, Chemistry, Biology and Medical Applications,' NATO Advanced Study Institute Series A: Vol. 26, eds. by R. T. Walker, E. DeClercq, F. Eukstein, Plenum Press, New York, 1979, p. 79.
7. 8-Methylselenoadenosine was prepared by treatment of 2 with methyl iodide in the presence of base.
8. M. Ikehara, M. Kaneko, Y. Nakahara, S. Yamada and S. Uesugi, *Chem. Pharm. Bull.*, 1961, **19**, 1381.

9. K. K. Ogilvie and L. Slotin, J. Chem. Comm., 1972, 646.
10. Satisfactory elemental analysis was obtained for all new compounds.
11. L. B. Townsend and G. H. Milne, J. Heterocyclic Chem., 1976, 13, 745.

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