Synthesis of a Novel Selenium-bridged Cyclonucleoside, *Se*^{2},2′-Cyclo-2-selenocytidine

By DEAN S. WISE and LEROY B. TOWNSEND*†

(*Department of Chemistry and Department of Medicinal Chemistry, University of Utah, Salt Lake City, Utah* 84112)

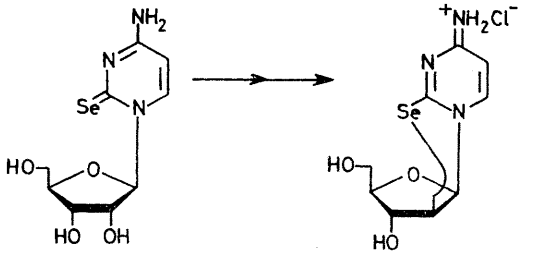
Summary The syntheses of 2-selenocytidine (**1**) and *Se*^{2},2′-cyclo-2-selenocytidine hydrochloride (**2**) are described.

SINCE the first oxygen-bridged cyclonucleosides were reported,[1] pyrimidine cyclonucleosides have proved to be key intermediates in the synthesis of biologically active compounds. Recent reports[2] on increased chemotherapeutic activity for ara-c in the anhydro form (*O*^{2},2′-cyclocytidine) have renewed interest in the synthesis of pyrimidine cyclonucleosides as potential chemotherapeutic agents and as versatile intermediates in the synthesis of other pyrimidine nucleosides modified at the C-2 position of the heterocycle and/or various positions of the carbohydrate unit. Sulphur-bridged cyclonucleosides have also shown great potential as key intermediates in syntheses which involve transformations in the carbohydrate portion of the molecule, *e.g.*, hydrolysis and desulphurization of the first reported[3] pyrimidine sulphur–cyclonucleoside, *S*^{2},2′-cyclo-2-thiothymidine, afforded thymidine. We have been[4] involved in the synthesis and chemistry of pyrimidine nucleosides which contain exocyclic selenium atoms, and we here report on the first synthesis of a selenium-bridged cyclonucleoside, *Se*^{2},2′-cyclo-2-selenocytidine.

For the synthesis of a selenium-bridged cyclonucleoside, the most obvious approach appeared to be the 2-acetoxyisobutyryl chloride method[5] since this reagent proved to be very successful in the formation of *S*^{2},2′-cyclo-2-thiocytidine in reactions with 2-thiocytidine. This prompted us to synthesize the unreported 2-selenocytidine for use in these studies. This was accomplished by silylation of 2-selenocytosine[6] (12·5 mmol) with *NO*-bis-(trimethylsilyl)acetamide and subsequent condensation[7] of the silylated heterocycle with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (13·75 mmol), in 1,2-dichloroethane in the

† *Current address:* Department of Medicinal Chemistry, College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109.

presence of 1·5 equiv. of stannic chloride. T.l.c. monitoring of the reaction indicated that only a single nucleoside was formed and that the reaction was complete after 3 h. The blocking groups were removed with methanolic ammonia at room temperature, and the resulting residue was purified by dry-column chromatography (SilicAR CC-7) eluting with chloroform–methanol (10:1). The fractions containing the product were evaporated to a syrup. Recrystallization of the yellow residue from methanol gave 2-selenocytidine (**1**) (31%): m.p. 142—143 °C



(1) (2)

(decomp.); u.v. λ_{max} (MeOH) in nm ($\epsilon \times 10^{-3}$) 252 (11·8) and 306 (12·7); pH 1, 235 (16·5); pH 11, 251 (18·8) and 299 (12·7); ^{1}H n.m.r. [$(CD_3)_2SO$] δ 6·93 (1H, 1′-H, d, $J_{1',2'}$ 2 Hz), 6·23 (1H, 5-H, d, $J_{5,6}$ 8 Hz), and 8·30 (1H, 6-H, d, $J_{5,6}$ 8 Hz).‡ The anomeric configuration and actual site of ribosylation were easily established by treatment of (**1**) with dilute base to afford a nucleoside which was identical with an authentic sample of the naturally occurring nucleoside cytidine.

The synthesis of the cyclonucleoside was accomplished when 2-selenocytidine (**1**) (0·42 mmol) was treated with acetonitrile (4 ml) containing 2-acetoxyisobutyryl chloride (2·4 mmol). The solution was stirred at room temperature for 3 h, filtered, 100 ml of diethyl ether added, and the resulting precipitate, which was predominantly the 5′-dioxolanone ether,[5] was collected by filtration and washed with diethyl ether. This solid, without purification, was then treated with 10 ml of 0·18 N methanolic hydrogen chloride at room temperature for 5 h, evaporated to dryness, and the residue crystallized from methanol to furnish *Se*^{2},2′-cyclo-2-selenocytidine hydrochloride (**2**): (64%); m.p. 205—206 °C; u.v. λ_{max} (H_2O) in nm ($\epsilon \times 10^{-3}$): 248 (22·7); pH 1, 248 (26·6); pH 11, 248 (24·3); ^{1}H n.m.r, [$(CD_3)_2SO$] δ 6·56 (1H, 1′-H, d, $J_{1',2'}$ 7 Hz), 8·06 (1H, 6-H, d, $J_{5,6}$ 8 Hz), and 6·75 (1H, 5-H, d, $J_{5,6}$ 8 Hz). Cyclonucleoside formation was supported by the expected wavelength shifts in the u.v. spectra as well as the upfield shift observed for the anomeric proton of (**2**) in comparison[8] to the chemical shift of the anomeric proton of (**1**).

We have found[9] that reactions such as deselenation or nucleophilic displacement of exocyclic alkylselenides in purine nucleosides generally occur under much milder conditions than required for the corresponding sulphur analogues. These reactions are being studied for (**2**).

We thank the National Cancer Institute, Department of Health, Education and Welfare for support.

(*Received* 30*th August* 1978; *Com.* 944.)

‡ Satisfactory elemental analysis was obtained for all new compounds.

[1] For a review of cyclonucleosides see: J. J. Fox, B. A. Otter, J. A. Rabi, and R. S. Klein, 'Lectures in Heterocyclic Chemistry,' Vol II, p. S-1, eds. R. N. Castle and L. B. Townsend, HeteroCorp, Orem, Utah, 1974; B. Capon, *Chem. Rev.*, 1969, **69**, 407; J. J. Fox, *Pure Appl. Chem.*, 1969, **18**, 112; M. Ikehara and T. Ueda, *Yaki Gosei Kagaku Kyohai Shi*, 1974, **32**, 402.

[2] M. A. Burgess, G. P. Bodey, R. A. Minow, and J. A. Gottlieb, *Cancer Treatment Reports*, 1977, **61**, 438; and references cited therein.

[3] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1959, 50.

[4] D. S. Wise and L. B. Townsend, *J. Heterocyclic Chem.*, 1972, **9**, 1461; D. S. Wise, G. H. Milne, and L. B. Townsend, 1976 Pacific Conf. on Chemistry and Spectroscopy, Nov. 8—10 1976, Phoenix, Arizona, cont. No. 20.

[5] A. I. Russell, M. Prystasz, E. K. Hamamura, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, 1974, **39**, 2182.

[6] H. G. Mautner, *J. Amer. Chem. Soc.*, 1956, **78**, 5292.

[7] U. Niedballa and H. Vorbruggen, *Angew. Chem. Internat. Edn.*, 1970, **9**, 461.

[8] D. S. Wise and L. B. Townsend, *Tetrahedron Letters*, 1977, 755.

[9] L. B. Townsend and G. H. Milne, *Ann. New York Acad. Sci.*, 1975, **255**, 91 and references cited therein; G. H. Milne and L. B. Townsend, *J. Heterocyclic Chem.*, 1976, **13**, 745.