Pyrrolopyrimidine Nucleosides. XIII. Synthesis and Chemical Reactivity of Certain Selenopyrrolo[2,3-*d*]pyrimidine Nucleosides (1) (2)

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5-Cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-selone (**1**) has been prepared *via* a reaction of the appropriate 4-chloro compound with sodium hydrogen selenide. Alkylation of **2** under basic conditions has provided certain 4-substitutedseleno-5-cyano-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidines. 5-Cyano-4-methylseleno-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine was allowed to react with hydroxylamine and hydrazine. The products obtained and reaction course were compared to those obtained from identical reactions using the corresponding sulfur analog.

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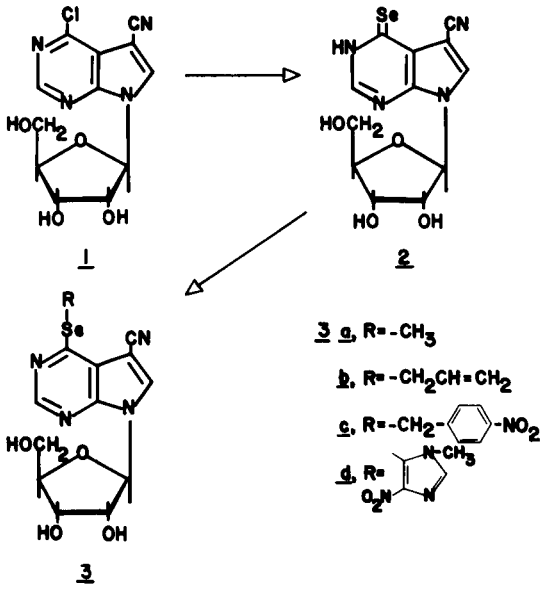
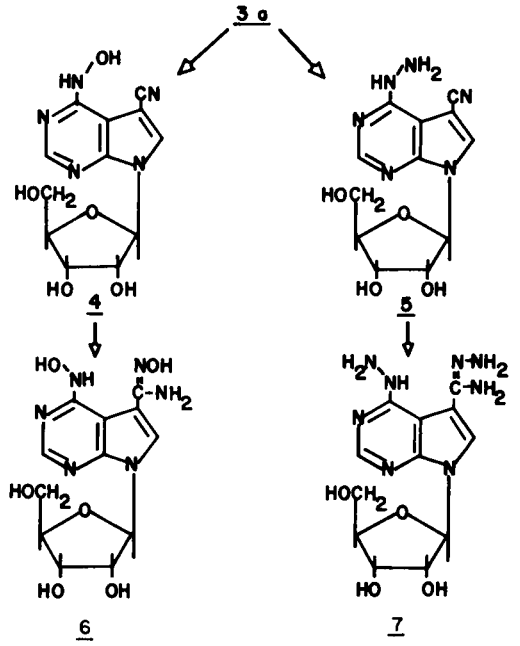
The effect of exocyclic substituents on the chemical reactivity of the cyano group of 5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidines has been studied extensively in our laboratory (3,4). We have also been involved in the synthesis of selenonucleosides (5,6) as potential anticancer agents and on the use of selenium *vs* sulfur in our synthesis program. It seemed of interest to combine both areas. This prompted us to investigate the synthesis of 5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-selone and certain 4-substitutedseleno derivatives in order to not only study the chemical reactivity of the 5-cyano group but also to study the relative reactivity of the 4-substitutedseleno group and the 5-cyano group toward nucleophilic reagents such as hydrazine and hydroxylamine.



4-Chloro-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (4) (**1**) was allowed to react with sodium hydrogen selenide in methanol at reflux temperature to furnish a crystalline nucleoside material which was characterized as 5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-selone (**2**). The uv spectrum revealed a very significant bathochromic shift to λ max (*p*H 1) 355 nm (**1**, λ max (*p*H 1) 274 nm). The pmr spectrum of **2** revealed a sharp singlet at δ 8.6 (C-2 proton), a sharp singlet at δ 8.3 (C-6 proton), a doublet centered at δ 6.2 for the anomeric proton), (H-1′) as well as the pattern of peaks usually observed (7) in the δ 3.5 to 5.0 reagion for the carbohydrate moiety.

Alkylation of **2** under basic conditions in methanol with methyl, allyl, *p*-nitrobenzyl, and 1-methyl-4-nitroimidazo-5-yl halides furnished the corresponding 4-methylseleno-(**3a**), 4-allylseleno- (**3b**), 4-*p*-nitrobenzylseleno- (**3c**), and 4-(1-methyl-4-nitroimidazol-5-yl)seleno- (**3d**), pyrrolo-[2,3-*d*]pyrimidine ribosides. The spectral data revealed a large hypsochromic shift for these 4-substitutedseleno compounds in comparison to the λ max values observed for **2**. This hypsochromic shift has been established (8) as proof that alkylation has occurred on the exocyclic seleno group rather than a ring nitrogen.

To study the selectivity of the exocyclic groups toward nucleophilic reagents, we allowed 5-cyano-4-methylseleno-



7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**3a**) to react with hydroxylamine in 2-propanol at reflux temperature. The reaction mixture was carefully monitored by uv spectroscopy and tlc against authentic samples of the probable products. The first product to be detected in the reaction mixture was established (9) as 5-cyano-4-hydroxylamine-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**4**). This established that a preferential nucleophilic displacement of the 4-methylseleno function by hydroxylamine had occurred. This was unexpected in view of previous work from our laboratory (4) where 4-methylthio-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine had been allowed to react under identical reaction conditions to furnish 4-methylthio-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine-5-carboxamidoxime. Therefore, the reaction of hydroxylamine with the 5-cyano group, in preference to displacement of the exocyclic 4-methylthio group, has demonstrated that the exocyclic 4-methylseleno function must be a better leaving group than the 4-methylthio group under the same reaction conditions. The final product to be obtained from the reaction (in the presence of excess hydroxylamine and more strenuous reaction conditions) was determined (9) to be 4-hydroxylamino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime (**6**) as the only product present in the reaction mixture. Therefore, addition to the 5-cyano function had occurred, but only after the more labile 4-methylseleno group had been displaced. This prompted us to corroborate this order of reactivity by using another nucleophile.

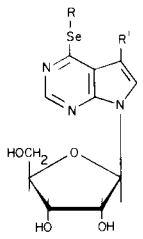
Treatment of **3a** with hydrazine in ethanol at reflux temperature furnished an intermediate product which was identified (9) as 5-cyano-4-hydrazino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (**5**). This intermediate (**5**) was then converted, *in situ*, to 4-hydrazino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidrazone (**7**) as the final product. This served to further demonstrate that the 4-methylseleno function was more reactive toward nucleophilic reagents than the 4-methylthio group and also in this particular instance the 5-cyano group. Therefore, the 4-substitutedseleno compounds prepared in this investigation proved to be of limited value in studying the chemical reactivity of the 5-cyano group due to their facile nucleophilic displacement. However, this study has provided evidence that selenium may have a definite place in synthetic organic reactions which require the mildest reaction conditions possible due to the presence of other labile functional groups.

EXPERIMENTAL

Proton magnetic resonance (pmr) spectra were obtained with a Varian A56/60 spectrometer (solutions in DMSO-d_6 or DMSO-d_6/deuterium oxide with DSS as internal standard) with chemical

Table I

Ultraviolet Spectral Data for Certain Selenopyrrolo[2,3-*d*]pyrimidine Ribonucleosides



R	R′	λ max (*p*H 1)	ε x 10^{-3}	λ max (water)	ε x 10^{-3}	λ max (*p*H 11)	ε x 10^{-3}
H	CN	355	15.3	362	14.2	334	13.8
CH_3	CN	315	15.7	312	18.5	312	17.0
$CH_2CH{=}CH_2$	CN	314	15.8	312	20.4	313	17.8

shift values reported in δ, parts per million, relative to the internal standard. Ultraviolet spectra were recorded on a Beckman DK-2 spectrophotometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Evaporations were performed under reduced pressure at 40° with a rotary evaporator unless otherwise stated. The infrared spectra were determined in pressed potassium bromide discs with a Beckman IR-8 spectrophotometer. Thin-layer chromatography was run on glass plates coated (0.25 mm) with silica gel (SilicAR 7GF, Mallinckrodt) with compounds of interest being detected by uv lamp (mineralight, 254 nm).

5-Cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-selone (**2**).

4-Chloro-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**1**, 1.0 g.) was added to methanol (25 ml.) and the mixture was heated to reflux. A solution of 200 mg. of sodium methoxide in methanol (5 ml.) was saturated with dry hydrogen selenide gas and the resulting sodium hydrogen selenide solution was added to the above methanolic solution containing **1**. The reaction mixture was heated at reflux for 30 minutes. The solution was evaporated *in vacuo* to a foam which was then used without further purification in the alkylation reactions. To obtain pure **2**, the foam was dissolved in 20 ml. of boiling water and the solution was allowed to stand at 5° for 48 hours. The brown oily crystals were redissolved in boiling water (25 ml.) and the solution was allowed to stand at 5° for 24 hours. The yellow-orange crystalline solid was collected by filtration and dried at 110° *in vacuo* for 2 hours over drierite to furnish 500 mg. of **2**, m.p. >240° dec.; ir: ≃2250 cm^{-1} for -C≡N. The presence of water was verified by a pmr spectrum.

Anal. Calcd. for $C_{12}H_{12}N_4O_4Se \cdot 0.5\ H_2O$: C, 39.60; H, 3.58; N, 15.40. Found: C, 39.60; H, 3.47; N, 15.32.

5-Cyano-4-methylseleno-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (**3a**).

The solid foam obtained from **2** was added to methanol (20 ml.) containing sodium methoxide (200 mg.) and methyl iodide (460 mg.) was then added to the solution. The solution was allowed to stir at room temperature for 30 minutes and the *p*H of the solution was adjusted to 6-7 with glacial acetic acid. The selenium was collected by filtration and the filtrate evaporated *in vacuo* to afford a white solid which was recrystallized twice from methanol-water and dried at 110° *in vacuo* over drierite for 2 hours to furnish 900 mg. of **3a**, m.p. 186-187°; ir: ≃2250 cm^{-1} (C≡N).

Anal. Calcd. for $C_{13}H_{14}N_4O_4Se$: C, 42.30; H, 3.80; N, 15.20. Found: C, 42.31; H, 3.78; N, 15.00.

4-Allylseleno-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**3b**).

The procedure was the same as for **3a** except that 390 mg. of allyl bromide was used. The product was recrystallized from a methanol-water mixture followed by methanol to furnish, after drying at 110° *in vacuo* over drierite for 2 hours, 400 mg. of **3b**, m.p. 146-148°.

Anal. Calcd. for $C_{15}H_{16}N_4O_4Se$: C, 45.60; H, 4.06; N, 14.19. Found: C, 45.83; H, 4.08; N, 14.20.

4-*p*-Nitrobenzylseleno-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (**3c**).

The procedure was the same as for **3a** except that 700 mg. of *p*-nitrobenzyl bromide was used. The solid was recrystallized from methanol and then dried at 110° in vacuo over drierite for 2 hours to furnish 800 mg. of **3c**, m.p. 218-220°.

Anal. Calcd. for $C_{19}H_{17}N_5O_6Se$: C, 46.52; H, 3.47; N, 14.29. Found: C, 46.55; H, 3.43; N, 14.27.

4-(1-Methyl-4-nitroimidazol-5-yl)seleno-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**3d**).

The procedure was the same as for **3a** except that 520 mg. of 5-chloro-1-methyl-4-nitroimidazole was used. The pure product was obtained by crystallization of the residue from a methanol-water mixture and recrystallization of the solid from water to furnish, after drying at 110° *in vacuo* for 2 hours over drierite, 925 mg. of **3d**, m.p. >210°. The presence of water was verified by a pmr spectrum.

Anal. Calcd. for $C_{16}H_{15}N_7O_6Se \cdot 0.5\ H_2O$: C, 39.00; H, 3.27; N, 20.00. Found: C, 38.83; H, 3.28; N, 20.20.

The Reaction of 4-Methylseleno-5-cyano-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (**3a**) with Hydroxylamine.

Hydroxylamine (100 mg.) (10) was added to 100 mg. of **3a** in 2-propanol (10 ml.). The solution was heated at reflux for 4 hours during which time the reaction was carefully monitored by tlc and uv against authentic samples (9) of compounds **3a**, **4** and **6**. At the end of this reaction time, another 100 mg. portion of hydroxylamine was added and heating at reflux was continued for an additional 12 hours with continued monitoring of the reaction mixture by tlc and uv against authentic samples of only **4** and **6** since after 4 hours total reaction time, compound **4** was the only compound detected in the reaction mixture. At the end of the total 18 hour reaction time, compound **6** was the only product detected in the reaction mixture which established that **3a** had been converted to **4** which in turn had been converted to the final product **6**.

The Reaction of 4-Methylseleno-5-cyano-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*pyrimidine (**3a**) with Hydrazine.

Compound **3a** (100 mg.) was dissolved in 10 ml. of ethanol and 0.5 ml. of 97+% hydrazine was then added. The solution was heated at reflux for 8 hours with the reaction being carefully monitored by uv and tlc against authentic samples (9) of **3a**, **5** and **7**. The starting material **3a** was found to rapidly disappear with the concomitant appearance of compound **5**. At the end of 8 hours, only compound **7** could be detected in the reaction mixture.

REFERENCES AND NOTES

(1) A portion of this research has been presented; L. B. Townsend and G. H. Milne, *Proc. New York Acad. Sci.*, New York, N. Y., September 4-6 (1974) (Abstract #6).

(2) This research was supported by research contracts #NIH-NOI-CM-43806 and #NIH-NOI-CM-23710 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

(3) K. H. Schram and L. B. Townsend, *J. Chem. Soc., Perkin Trans. I*, 1253 (1975).

(4) B. C. Hinshaw, O. Leonoudakis, K. H. Schram and L. B. Townsend, *ibid.*, 1248 (1975) and references cited therein.

(5) G. H. Milne and L. B. Townsend, *J. Med. Chem.*, 17, 263 (1974).

(6) L. B. Townsend and G. H. Milne, Annals of the New York Academy of Sciences, 255, 91 (1975) and references cited therein.

(7) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 2, W. W. Zorbach and R. S. Tipson, Eds., John Wiley and Son, Inc., New York, N.Y., 1973, Chapter 7.

(8) G. H. Milne and L. B. Townsend, *J. Chem. Soc., Perkin Trans. I*, 2677 (1972).

(9) The uv and tlc comparisons for the nucleophilic displacement study were made against authentic samples of **4**, **5**, **6** and **7** prepared by a method described in reference 4.

(10) C. D. Hurd, *Inorg. Synth.*, 1, 87 (1939).