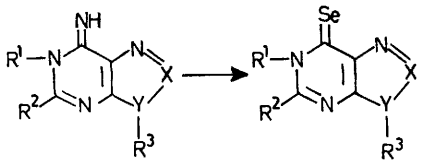
A Novel Synthesis of 6-Seleno-substituted Nucleosides, Nucleotides and Cyclic Nucleotides

By CHYNG-YANN SHIUE and SHIH-HSI CHU*
(*Division of Biological and Medical Sciences, Brown University, Providence, Rhode Island* 02912)

Summary Treatment of adenosine, 2-aminoadenosine, adenine arabinoside, formycin, 1-Me-AMP, cyclo-AMP, and 1-Me-cyclo-AMP with H_2Se in aqueous pyridine gave the corresponding seleno compounds with good yield.

CERTAIN selenopurine analogues have been found to have antitumour activity[1-8] These seleno-heterocycles were usually synthesized from the corresponding halo-heterocycles with either sodium hydrogen selenide or selenourea.[5,7,9,10] However, the chlorination of the carbonyl function in nucleobases is tedious, and during studies on the syntheses and biological activity of seleno-substituted nucleosides, nucleotides, and cyclic nucleotides,[2-5] we have found a novel preparation of selenoxo heterocycles by

displacement of the amino group in the heterocycle with hydrogen selenide (Scheme).



(I) (II)

SCHEME

(**a**); X=CH, Y=N, $R^1=R^2=H$, $R^3=\beta$-D-ribofuranosyl
(**b**); X=CH, Y=N, $R^1=H$, $R^2=NH_2$, $R^3=\beta$-D-ribofuranosyl
(**c**); X=CH, Y=N, $R^1=R^2=H$, $R^3=3',5'$-cyclic phosphoribosyl
(**d**); X=CH, Y=N, $R^1=Me$, $R^2=H$, $R^3=3',5'$-cyclic phosphoribosyl
(**e**); X=CH, Y=N, $R^1=Me$, $R^2=H$, $R^3=5'$-phosphoribosyl
(**f**); X=NH, Y=C, $R^1=R^2=H$, $R^3=\beta$-D-ribofuransoyl
(**g**); X=CH, Y=N, $R^1=R^2=H$, $R^3=$arabinofuranosyl

The amino heterocycle was heated at 65° with excess of H_2Se in pyridine–H_2O in a sealed tube. At the end of the reaction the tube was cooled and the solvent was evaporated. In the case of seleno-substituted nucleosides, the residue was dissolved in 3% Na_2CO_3 solution and filtered. The filtrate was acidified with HOAc, and the precipitates collected and washed with a small amount of water to give pure seleno heterocycles. For seleno-substituted nucleotides and cyclic nucleotides, the residue was dissolved in a small amount of water and then passed through a Dowex 50 (H^+) column. The compound was eluted with water. Evaporation of the appropriate fractions gave the pure seleno-nucleotides and cyclic nucleotides. The compounds were identified by elemental analysis, u.v. spectroscopy, t.l.c., and/or n.m.r. spectroscopy and compared with authentic samples. The results are listed in the Table.

This new method requires no prior protection of the sugar grouping and gives higher yield than conventional procedures. The selenium compounds can be readily converted to the two most important intermediates in synthetic purine chemistry, 6-chloropurine[11] and 6-methylselenopurine.[3] A variety of 6-substituted purine analogues can be readily prepared by nucleophilic displacement of the 6-chloro or 6-methylseleno group with suitable nucleophiles. It is interesting to note that H_2Se reacted with adenosine and cyclo-AMP to give a high yield of 6-selenoxo-9-(β-D-ribofuranosyl)purine[12] (IIa) and 6-selenoxo-9-(β-D-ribofuranosyl)purine 3′,5′-cyclic phosphate (IIc) while adenosine[13] and cyclo-AMP were relatively inert to H_2S under the same conditions. 1-Methyl compounds (1-Me-AMP and 1-Me-cyclo-AMP) failed to undergo Dimroth rearrangement to the N^6-methyl compounds[14] prior to Se displacement and yield the 1-Me derivatives (IId and IIe) rather than the unsubstituted purines (IIc). The scope of this new method is under investigation.

TABLE

Formation of 6-selenoxo-9-(β-D-ribofuranosyl)purine 3′,5′-cyclic phosphate and related compounds

Compound	Reaction time /days	Yield /%
6-Selenoxo-9-(β-D-ribofuranosyl)purine[12] (IIa)	5	56
2-Amino-6-selenoxo-9-(β-D-ribofuranosyl)-purine[3,6] (IIb)	4·5	21
6-Selenoxo-9-(β-D-ribofuranosyl)purine-3′,5′-cyclic phosphate (IIc)	4·5	36
1-Methyl-6-selenoxo-9-(β-D-ribofuranosyl)purine-3′,5′-cyclic phosphate (IId)	2	75
1-Methyl-6-selenoxo-9-(β-D-ribofuranosyl)-purine-5′-phosphate (IIe)	2	49
7-Selenoxo-3-(β-D-ribofuranosyl)pyrazalo[4,3-*d*] pyrimidine (Selenoformycin B[7] (IIf)[a]	1·5	32
6-Selenoxo-9-(β-D-arabinofuranosyl)-purine[5] (IIg)	3·5	22

[a] Formycin was supplied by Meizi Seika Ltd., Kawasaki, Japan.

We thank the United States Public Health Service for support and Drs. R. E. Parks, Jr. and P. Calabresi for encouragement.

(*Received*, 11*th February* 1975; *Com.* 161.)

[1] H. G. Mautner and J. J. Jaffe, *Cancer Res.*, 1958, **18**, 294; 1960, **20**, 81; H. G. Mautner, *Biochem. Pharmacol.*, 1958, **1**, 169; H. G. Mautner and J. J. Jaffe, *ibid.*, 1961, **5**, 343.
[2] H. G. Mautner, S. H. Chu, J. J. Jaffe, and A. C. Sartorelli, *J. Medicin. Chem.*, 1963, **6**, 36.
[3] S. H. Chu, *J. Medicin. Chem.*, 1971, **14**, 254.
[4] S. H. Chu and D. D. Davidson, *J. Medicin. Chem.*, 1972, **15**, 1088; S. H. Chu, C. Y. Shiue, and M. Y. Chu, *ibid.*, 1974, **17**, 406.
[5] S. H. Chu, C. Y. Shiue, and M. Y. Chu, *J. Pharm. Sci.*, in the press.
[6] L. B. Townsend and G. H. Milne, *J. Heterocyclic Chem.*, 1970, **7**, 753.
[7] G. H. Milne and L. B. Townsend, *J.C.S. Perkin I*, 1972, 2677.
[8] G. H. Milne and L. B. Townsend, *J. Medicin. Chem.*, 1974, **17**, 263.
[9] H. G. Mautner, *J. Amer. Chem. Soc.*, 1956, **78**, 5292.
[10] E. Dyer and L. E. Minnier, *J. Medicin. Chem.*, 1968, **11**, 1232.
[11] F. Bergmann and M. Rashi, *Israel J. Chem.*, 1969, **7**, 63.
[12] J. J. Jaffe and H. G. Mautner, *Cancer Res.*, 1959, **20**, 381.
[13] T. Veda, M. Imazawa, K. Miura, R. Iwata, and K. Odajima, *Tetrahedron Letters*, 1971, 2507.
[14] J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, 1963, **85**, 193.