

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

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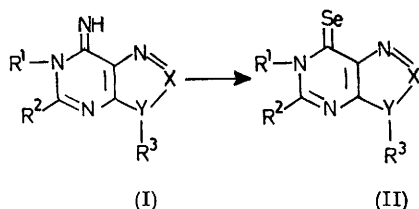
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Summary Treatment of adenosine, 2-aminoadenosine, adenine arabinoside, formycin, 1-Me-AMP, cyclo-AMP, and 1-Me-cyclo-AMP with H_2Se in aqueous pyridine gave the corresponding seleno compounds with good yield.

CERTAIN selenopurine analogues have been found to have antitumour activity¹⁻⁸ These seleno-heterocycles were

usually synthesized from the corresponding halo-heterocycles with either sodium hydrogen selenide or seleno-urea.^{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).



SCHEME

- (a); X=CH, Y=N, R¹=R²=H, R³=β-D-ribofuranosyl
 (b); X=CH, Y=N, R¹=H, R²=NH₂, R³=β-D-ribofuranosyl
 (c); X=CH, Y=N, R¹=R²=H, R³=3',5'-cyclic phosphoribosyl
 (d); X=CH, Y=N, R¹=Me, R²=H, R³=3',5'-cyclic phosphoribosyl
 (e); X=CH, Y=N, R¹=Me, R²=H, R³=5'-phosphoribosyl
 (f); X=NH, Y=C, R¹=R²=H, R³=β-D-ribofuranosyl
 (g); X=CH, Y=N, R¹=R²=H, R³=arabinofuranosyl

The amino heterocycle was heated at 65° with excess of H₂Se in pyridine-H₂O 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% Na₂CO₃ 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-chloropurine¹¹ and 6-methyl-

selenopurine.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 H₂Se reacted with adenosine and cyclo-AMP to give a high yield of 6-selenoxo-9-(β-D-ribofuranosyl)purine¹² (IIa) and 6-selenoxo-9-(β-D-ribofuranosyl)purine 3',5'-cyclic phosphate (IIc) while adenosine¹³

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)pyrazolo[4,3-d] pyrimidine (Selenoformycin B ⁷ (IIf) ^a	1-5	32
6-Selenoxo-9-(β-D-arabinofuranosyl)-purine ⁶ (IIg)	3-5	22

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

and cyclo-AMP were relatively inert to H₂S under the same conditions. 1-Methyl compounds (1-Me-AMP and 1-Me-cyclo-AMP) failed to undergo Dimroth rearrangement to the N⁶-methyl compounds¹⁴ 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.

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