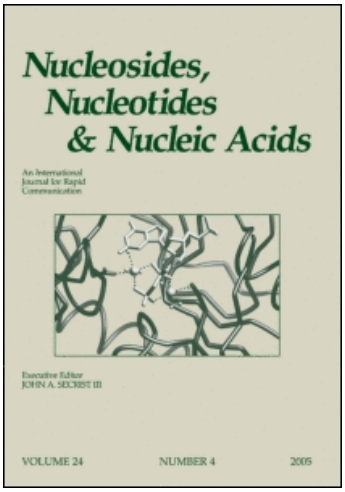


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Nucleosides Containing Selenium[1] II

Zbigniew J. Witczak[a]
[a] Department of Organic Chemistry, Medical Academy, Faculty of Pharmacy, Łodz, Narutowicza 120a, Poland

To cite this Article Witczak, Zbigniew J.(1983) 'Nucleosides Containing Selenium[1] II', Nucleosides, Nucleotides and Nucleic Acids, 2: 4, 295 — 318
To link to this Article: DOI: 10.1080/07328318308078864
URL: http://dx.doi.org/10.1080/07328318308078864

NUCLEOSIDES AND NUCLEOTIDES, 2(4), 295-318 (1983)

NUCLEOSIDES CONTAINING SELENIUM[1] II.

Zbigniew J. Witczak[2]

Department of Organic Chemistry, Medical Academy,
Faculty of Pharmacy, 90-145 Łodz, Narutowicza 120a Poland

CONTENTS

1. INTRODUCTION

The chemistry of nucleoside analogs[3] with antiviral and antitumor[4] activity is well known. These properties have prompted considerable attention to new developments in synthetic methodology, especially in the field of modification of heterocyclic functions. One such class of methods is introduction of sulfur and selenium into the purine or pyrimidine bases. While thio-substituted nucleosides[5,6] are well known, their selenium counterparts are relatively less known in contrast to their potential importance as antitumor agents, as has been reported.[7-14] The fact that the chemistry of selenium nucleosides is relatively unexplored encouraged review of the literature in this field.

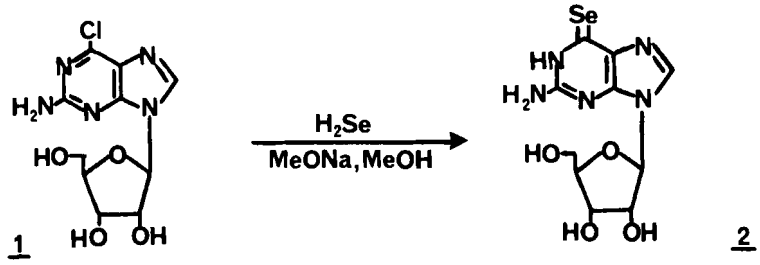
2. METHOD OF SYNTHESIS OF NUCLEOSIDE ANALOGS CONTAINING SELENIUM.

The first successful introduction of selenium into nucleosides was reported in 1960 and 6-selenopurines and 6-selenopurine ribonucleosides

 0732-8311/83/0204-0295$3.50/0

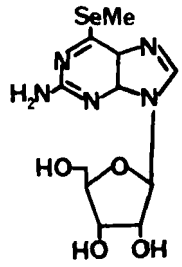
were tested as antitumor agents.[10] Unfortunately, the 6-selenopurines as well as the 6-selenopurine-9-β-D- ribonucleosides are highly unstable[10] under neutral and basic conditions in contrast to 6-selenoguanosine[11] which is essentially stable under these conditions.

Instability of the selenium congeners is a great difficulty in synthesis. The first method of preparation of selenonucleosides was based on the general procedure for the synthesis of selenopurines and selenopyrimidines, reported in 1956 by Mautner[7] and coworkers[8-10] Townsend and Milne[11,12] and Chu[13,14] independently described the synthesis of 6-selenoguanosine (2) by treatment of 2-amino-6-chloro-9-β-D-ribofuranosylpurine (1) with a methanolic solution of sodium hydrogen selenide at reflux temperature for 15 min. Treatment of (1) with selenourea also afforded 6-selenoguanosine (2) in 62% yield.[14] This is the first example of application of selenourea in nucleoside synthesis.

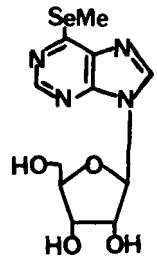


Stabilization and purification of 6-selenoguanosine (2) by recrystallization from acetate buffer using ascorbic acid as an antioxidant has also been reported.[15] A lyophilized parenteral dosage form of 6-selenoguanosine (2) purified by the above method suitable for experimental evaluation of its anticancer activity has also been prepared.[15]

An interesting report on the oxidative degradation of 6-selenoguanosine (2) has been published by Repta and coworkers.[16] This reaction proceeds in the presence of oxygen via a diselenide intermediate with the formation in the final stage of a selenide and metallic selenium. Above degradation pathway was different[16] from that reported for the oxidation of related thio congeners. Treatment of (2) with methyl iodide under basic conditions afforded 6-methylselenoguanosine (3).[13] Similarly, 6-methylselenoinosine[13] (4) has been synthesized.

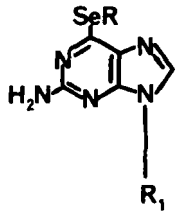


3



4

It is noteworthy that both selenonucleosides (3) and (4) are more stable than the corresponding 6-selenoguanine and 6-selenoguanosine. Moreover 6-selenoguanosine (2) is more soluble[13] than selenoguanine and the thio congener, 6-thioguanine.



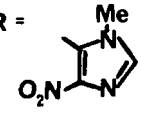
R_1 = ribofuranosyl

2 a R = 

b R = $-CH_2CH{=}CH_2$

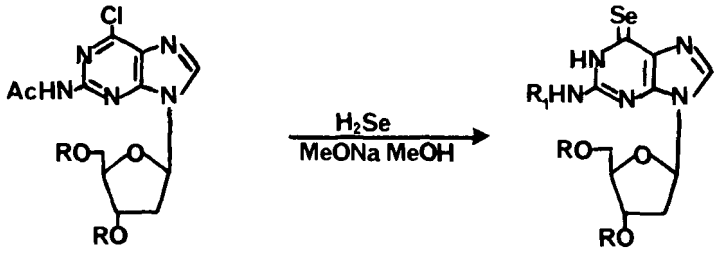
c R = $-CH_2Ph$

d R = $-CH_2C_6H_4NO_2$-p

e R = 

Alkylation of (2) with several alkylating agents occurred at the exocyclic 6-seleno group with formation 6-alkylseleno-2-amino-9-β-D-ribofuranosyl purines as reported by Milne and Townsend.[12]

Milne and Townsend[17,18] as well as Chu and Davidson[19] independently report the synthesis of both α and β anomers of 2'-deoxy-6-selenoguanosine by treatment of 2-acetamido-6-chloro-9-(2'-deoxy-3',5'-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)-9H-purine (5) and its α anomer (6) with alcoholic sodium methoxide and hydrogen selenide.



5 R = p-toluoyl

6 α-anomer

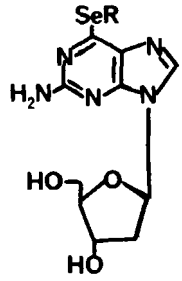
7 R = p-toluoyl, R_1=H

8 R = R_1=H

α-anomers { 9 R = p-toluoyl, R_1=Ac
10 R = R_1=H

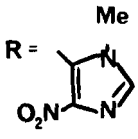
According to the results of Chu and Davidson[19] the β-anomer (5) required extended time (3 days) of reaction with hydrogen selenide, whereas the α-anomer (6) required only 80 min at room temperature. However, the formation of partially protected precursor (7) of β-2'-deoxy-6-selenoguanosine (8) as well as precursor (9) of α-2'-deoxy-6-selenoguanosine (10) has been observed. Treatment of (7) and (9) with methanolic sodium methoxide gave anomers (8) and (10) in 59% and 70% yields, respectively.[19] Unfortunately both α and β-anomers (10) and (8) are unstable in aqueous solution and decompose at room temperature after 24h.

Alkylation of (8) and (10) with several alkylating agents afforded alkyl derivatives[18] as illustrated, for the β anomer.

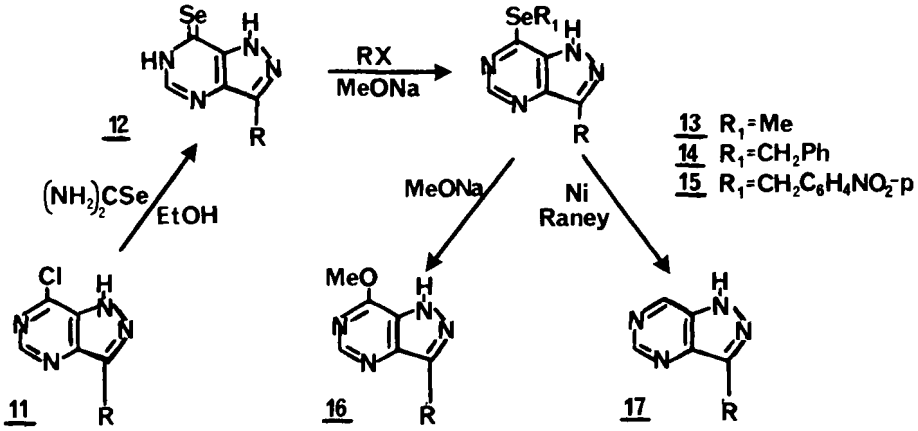


8 a R = Me

b R = $CH_2C_6H_4NO_2$-p

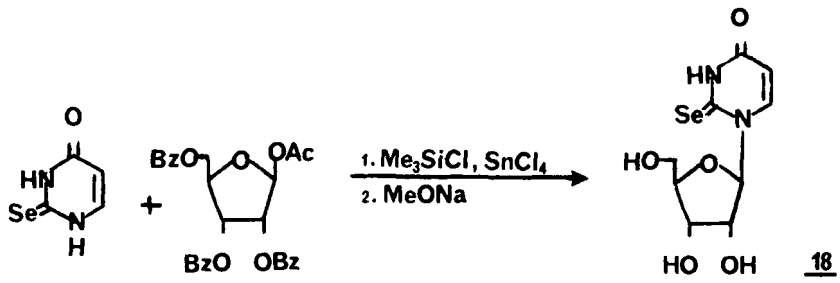
c R = 

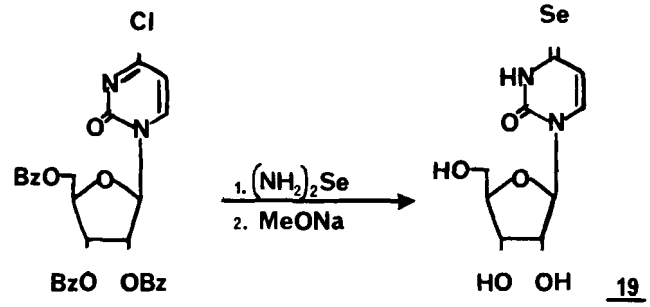
Milne and Townsend[20] also reported the synthesis of selenoformicin B, i.e., 7-selenoxo-3-(β-D-ribofuranosyl)-pyrazolo[4,3-d]-pyrimidine (12) by nucleophilic displacement of the chloro group from 7-chloro-3-(β-D-ribofuranosyl)-pyrazolo-[4,3-d]-pyrimidine (11) with selenourea in ethanol at reflux temperature. Alkylation of (12) with methyl iodide, benzyl bromide, as well as α-bromo-p-nitrotoluene in methanolic sodium methoxide solution afforded alkylseleno derivatives (13), (14), and (15), respectively. Nucleophilic displacement of an alkylseleno group in (13) with methanolic sodium methoxide at reflux for 24 h gave 7-methoxy-3-(β-D-ribofuranosyl)-pyrazolo-[4,3-d]pyrimidine (16). However, removal of the methylseleno group from (13) with Raney nickel is also difficult and requires 24 h of reflux. The unexpected stability of (13) toward basic conditions and the difficulty encountered in removal of the methylseleno group from (13) could be explained by the formation of the anion of (13) by removal of the NH proton from the pyrazole group.



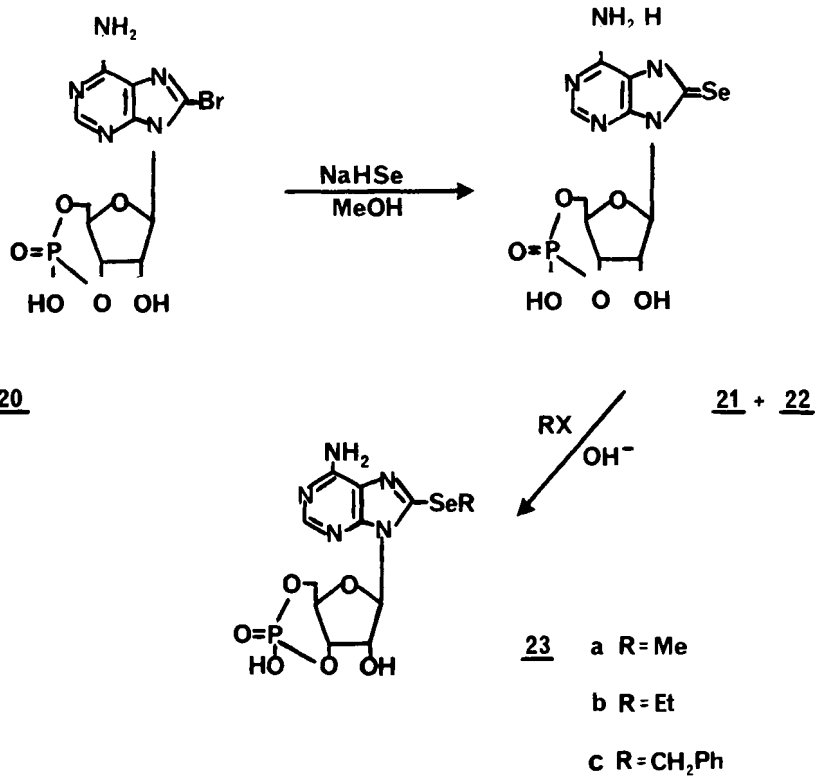
The synthesis of 2-seleno- and 4-selenouridine has been reported by Wise and Townsend.[21,22] The synthetic approach to 2-selenouridine (18) begins with silylation of 2-selenouracil, followed by condensation with 2,3,5-tri-O-benzoyl-1-O-acetyl-α-D-ribofuranose. Deprotection of the

condensation product with sodium methoxide in methanol afforded 2-selenouridine (18) in 30% yield. The synthetic approach to 4-selenouridine (19) starts from the 4-chloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrimidine-2-one, which on treatment with selenourea in methanol at reflux for 2 h, and subsequent debenzoylation with sodium methoxide in methanol at room temperature afforded 4-selenouridine (19). The seleno group of (18) and (19) is very labile according to the observations of these authors.[21,22]

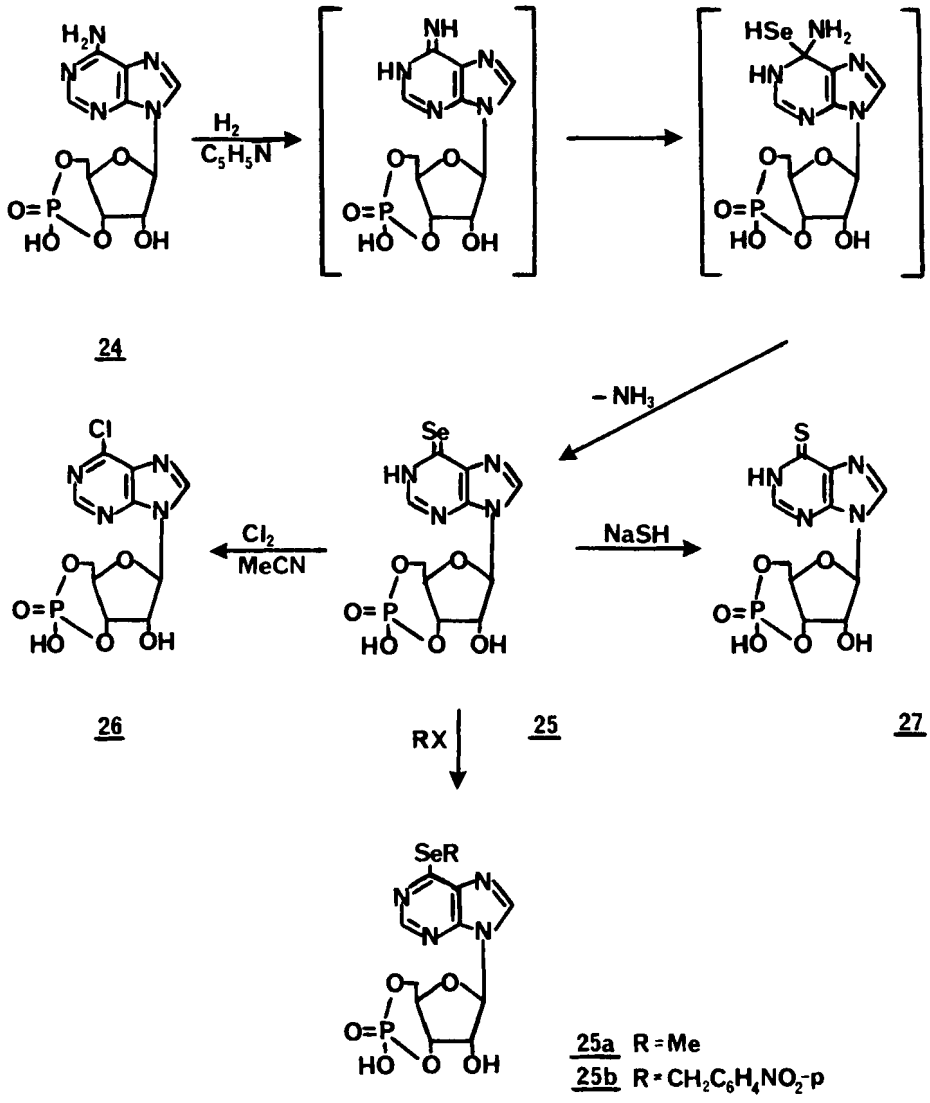




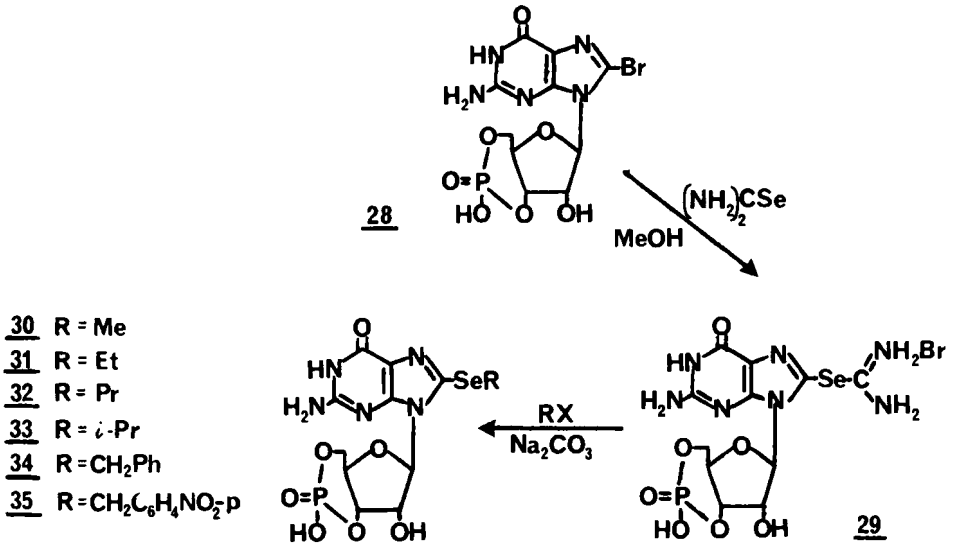
In 1974 Chu and coworkers[23] first reported the synthesis of some 8-substituted seleno cyclic nucleotides (23a-c) by treatment of 8-bromoadenosine 3',5'-cyclic monophosphate (20) with sodium hydrogen selenide in refluxing methanol and subsequent alkylation. However, a simultaneous formation of 8-seleno-cAMP (21) together with cAMP (22) in ratio 1:2 was observed. Treatment of (20) with selenourea under the same conditions did not afford (21).



An interesting synthetic approach has been developed for the synthesis of 6-selenoxo-9-(β-D-ribofuranosyl)purine 3',5'-cyclic phosphate (25) and the selenoalkyl analogs[24] (25a) and (25b), using as a starting material the 6-amino precursor, (24) which on treatment with hydrogen selenide in aqueous pyridine at 65° for 1.5-5 days gave the corresponding 6-seleno derivative (25). The proposed mechanism of this displacement proceeds by tautomerization of amino to imino, followed by addition of hydrogen selenide and then elimination of ammonia with the formation of (25). Alkylation of (25) affords (25a) and (25b) in moderate yields whereas chlorination with chlorine in acetonitrile gave 6-chloro-9-(β-D-ribofuranosyl)purine 3',5'-cyclic phosphate (26). Treatment of (25) with hydrogen sulfide aqueous basic solution gave 6-thio-9-(β-D-ribofuranosyl)purine,3',5'-cyclic phosphate (27).

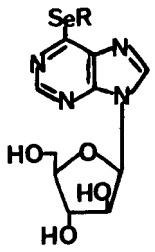


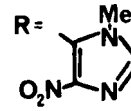
8-Selenoguanosine cyclic 3',5'-phosphate derivatives (30)-(35) have also been synthesized[25] using as starting material cGMP which by direct bromination gave 8-bromo-cGMP (28). Treatment of (28) with selenourea in refluxing methanol gave the isoselenouronium hydrobromide salt (29) as an intermediate. Alkylation of (29) yielded the corresponding alkylated nucleotides (30)-(35) respectively. Analogously, 8-substituted selenoguanosine 5'-monophosphates and selenoguanosines were synthesized.[25]



Biochemical synthesis of nucleotides containing selenium has also been reported.[26-30] Recently it has been reported that radioactive selenium ^{75}Se could be incorporated into Escherichia coli tRNA, resulting in the formation of 4-selenouracil instead of the normal 4-thiouracil.[26,27] Suggestion that selenium incorporation had occurred by the known pathway of sulfur transfer to a specific uracil residue of Escherichia coli tRNA[26] has recently been questioned.[28] Synthesis of selenium containing tRNAs by a process highly specific for selenium has been demonstrated in anaerobic bacterium Clostridium sticklandi.[29] This synthesis is reminiscent of one reported earlier.[30]

Chu and coworkers[31] also prepared and tested a series of 6-substituted 6-seleno-purine arabinosides, using the approach previously described.[20-25]

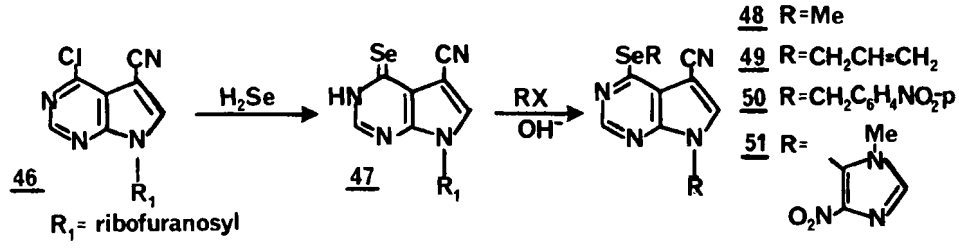


36 R=Me
37 R=Et
38 R=Pr
39 R=i-Pr
40 R=n-Bu
41 R=CH2Ph
42 R= 
43 R=CH2CH=C(CH3)2
44 R=CH2C6H4NO2-p
45 R= 

Shiue and Chu[32] report a facile synthesis of 1-β-D-arabinofuranosyl-2-seleno- and 4-selenouracil derivatives using the methodology previously established.[24] 2-Selenouridine (18) as well as 4-selenouridine (19) which were previously synthesized[21,22] also have been prepared by a modification of the above method using dimethylformamide instead of ethylene glycol monomethyl ether as solvent.

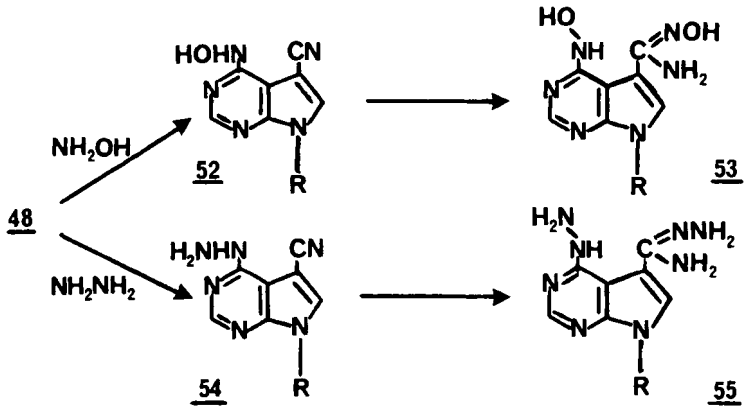
Shiue and Chu[33] also described a new and efficient method of synthesis of 6-seleno-substituted nucleosides, and nucleotides, as well as cyclic nucleotides, by displacement of the amino group in the heterocycle with hydrogen selenide in aqueous pyridine solution (at 65° in a sealed tube) in 22-75% yield. This method has been reported previously[18] for the synthesis 6-seleno-9-(β-D-ribofuranosyl) purine 3',5'-cyclic phosphate (24). According to the authors[33], these modifications require no prior protection of the sugar grouping and also give higher yield than conventional procedures.

Chu and coworkers[34] have developed a very convenient and simple method of alkylation of thio- and selenonucleosides with dialkyl disulfides or diselenides in the presence of tri-n-butylphosphine in dimethylformamide at room temperature. Milne and Townsend[35] have accomplished the synthesis of the 4-seleno-5-cyano-7-(β-D-ribofuranosyl)-pyrrolo-[2,3-d]-pyrimidines (48)-(51) as illustrated. Similarly 7-(β-D-ribofuranosyl)pyrrolo-[2,3-d]-pyrimidin-4-selone[36] has been synthesized.



Reactivity of the 4-substituted seleno group and the 5-cyano group in (48) towards nucleophilic reagents such as hydrazine and hydroxylamine has been reported.[35] Treatment of (48) with hydroxylamine in 2-propanol at reflux furnished intermediate (52) which was then converted in situ to 4-hydroxylamino-7-(β-D-ribofuranosyl)-

pyrollo-[2,3-d]pyrimidine-5-carboxamidoxime (53) as the only product present in the reaction mixture.

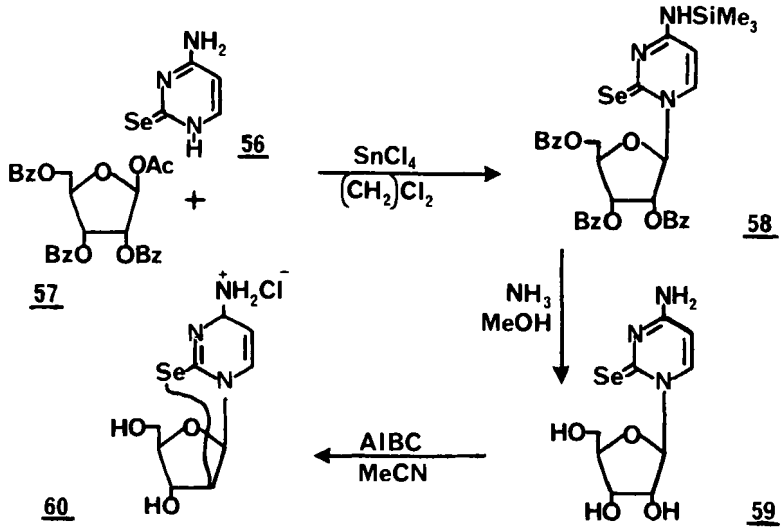


R=ribofuranosyl

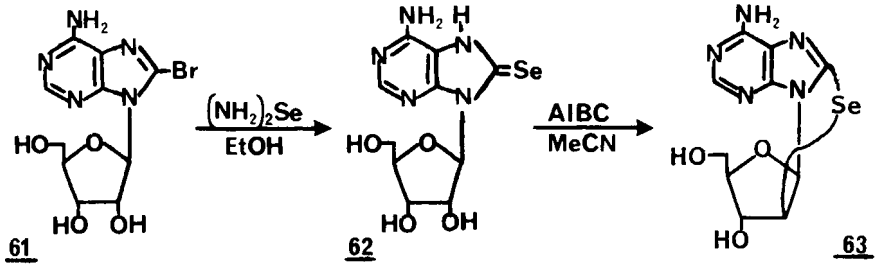
Similarly, treatment of (48) with hydrazine under the same condition gave intermediate (54) which was converted to 4-hydrazino-7-(β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine-5-carboxamidrazone (55). The configuration (Z or E) of (53) and (55) has not been established.

Wise and Townsend[37] also report the effects of exocyclic atoms (O, S, Se) in nucleosides on the chemical shifts of the anomeric proton in the sugar moieties as well as protons at C-5 and C-6 position of the hetero ring of a selected series of compounds such as 4-thio and 4-selenouracil, and 2,4,-dithio and 2,4-diselenouracil.

In 1979 Wise and Townsend[38] reported the first synthesis of a selenium bridged cyclonucleoside, Se',2'-cyclo-2-selenocytidine, using as starting material 2-selenocytosine[6] (56). Silylation of (56) with N,O- bis-(trimethylsilyl)acetamide and subsequent condensation with 1-O-acetyl- 2,3,5-tri-O-benzoyl-D-ribofuranose (57) in 1,2-dichloroethane in the presence of stannic chloride afforded a silylated nucleoside (58). Deprotection of (58) with methanolic ammonia at room temperature yielded 2-selenocytidine (59). Treatment of (59) for 3 h at room temperature with acetonitrile containing 2-acetoxyisobutyryl chloride afforded Se'-2'-cyclo- 2-selenocytidine hydrochloride (60) in 64% yield.



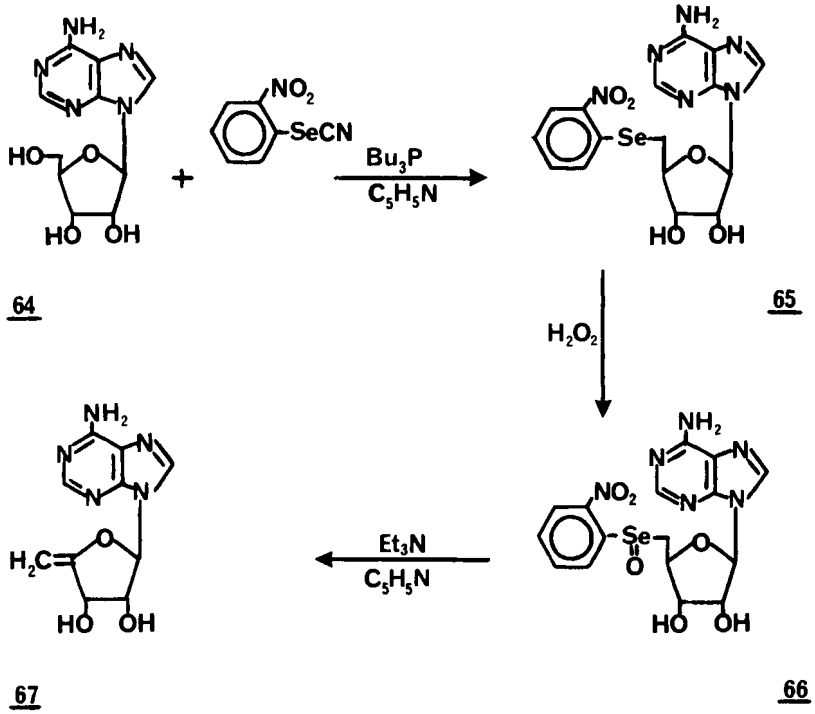
Synthesis of Se^8,2'-cyclo-8-seleno-9-β-D-arabinofuranosyladenine (63) has also been reported.[39] This synthetic approach starts from 8-bromoadenosine (61) which by treatment with selenourea in absolute ethanol afforded 8-selenoadenosine (62). Treatment of (62) with 2-acetoxyisobutyryl chloride in acetonitrile solution furnished first cyclic selenopurine nucleoside Se^8,2'-cyclo-8-seleno-β-D-arabinofuranosyladenine (63) in 54% yield.



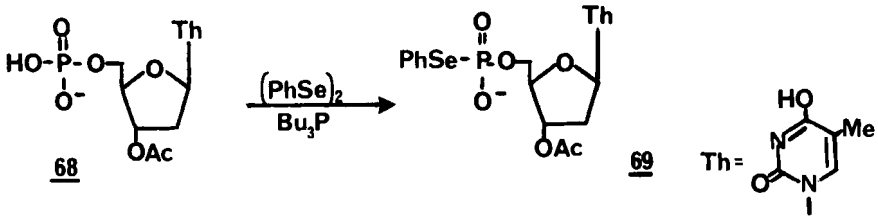
Recently pure 8-selenoadenosine (62) has been prepared[40] by heating 8-bromoadenosine with selenourea in boiling 1-propanol.

Recently Takaku and coworkers[41] reported the synthesis of 5'-Se (2-nitrophenyl)-5'-selenoxyadenosine (66) as an intermediate to the corresponding 9-(5'-deoxy-β-D-erythro-pent-4-eno-furanosyl)-adenine

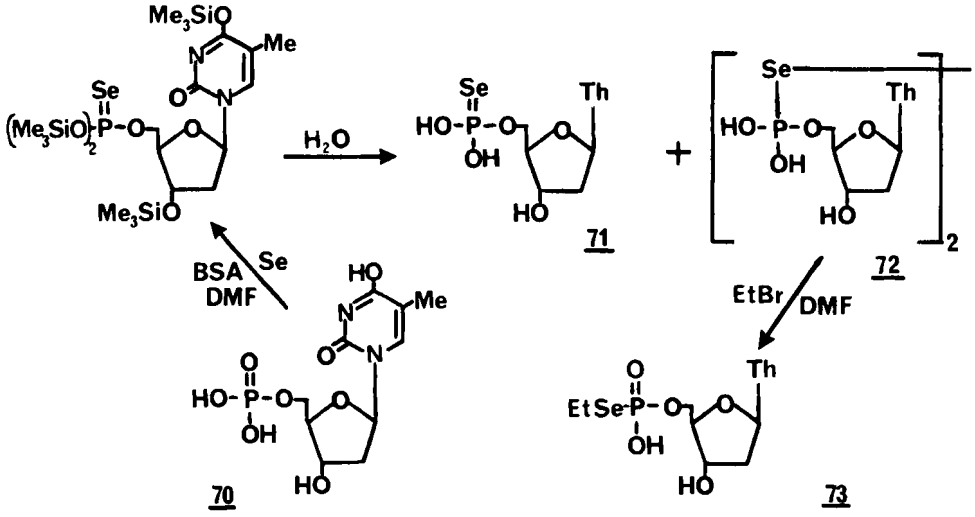
(67). Treatment of adenosine (64) with 2-nitrophenylselenocyanate and tri-n-butylphosphine gave selenide (65)[43] which on oxidation with an excess of hydrogen peroxide afforded selenoxide (66). Treatment of (66) with triethylamine in pyridine yielded (67) in very good yield (90%). This result shows that triethylamine effectively promotes syn elimination of the selenoxide group and hydrogen at the 4' position and is similar to the reaction previously reported by Zylber and coworkers.[42]



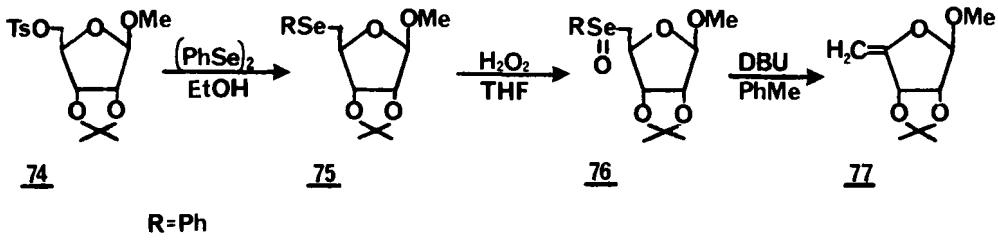
Tri-n-butylphosphine as a combined reagent together with diphenyl diselenide in acetonitrile solution has been reported[43] for the preparation of the new type selenonucleotides i.e. 3'-O-acetylthymidine, Se-phenyl-5'-phosphoroselenoate (69). This sequence starts from the corresponding monopyridinium salt of 3'-acetylthymidine-5'-phosphate (68).



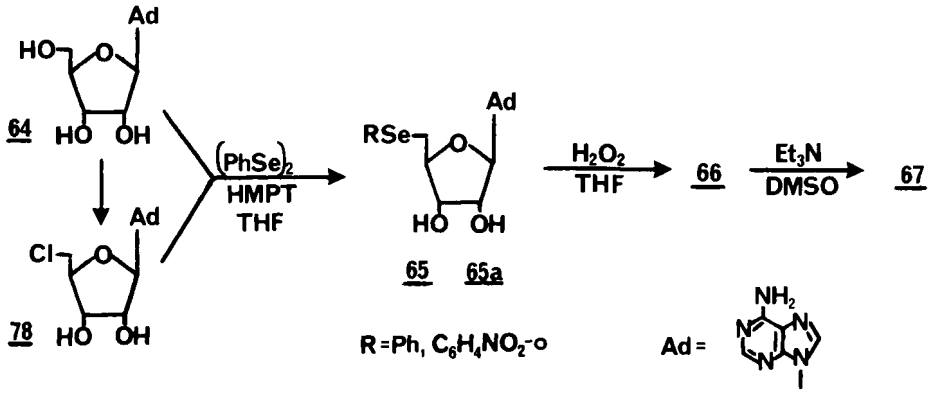
It is noteworthy that treatment of thymidine 5'-phosphate (70) in the presence of BSA [bis(trimethylsilyl)-acetamide] in dimethylformamide solution with selenium powder afforded the mixture of two products, thymidine 5'-phosphoroselenoate (71) and its autooxidized product (72) having an Se-Se bond, in the ratio 1:8. Alkylation of the above mixture with ethyl bromide in dimethylformamide solution afforded Se-ethylthymidine-5'-phosphoroselenoate (73).



Recently Zylber, Gaudemer and coworkers[44] reported the synthesis of (67) by a procedure which has been previously employed for the synthesis of methyl-5-deoxy-2,3-O-isopropylidene-β-D-erythro-pent-4-enofuranoside (77) and nucleoside (67)[42]. The synthesis of (77) starts with methyl-2,3-O-isopropylidene-5-p-tolylsulfonyl-β-D-ribofuranoside (74).



Synthesis of (67) starts with adenosine (64) or 5'-deoxy-5'-chloroadenosine (78).



9-(5-Deoxy-2,3-O-isopropylidene-β-D-erythro-pent-4-enofuranosyl) adenine[44] has been synthesized in the same manner as (67) and (77).

S_N2 nucleophilic displacement of the p-tolylsulfonyl group in (74) as well as chlorine in (78) has been accomplished by treatment with diphenyl diselenide. However, the S_N2 nucleophilic displacement of the p-tolylsulfonyl group at C-5 on the furanose ring with selenocyanate ion has been reported by Van Es and Whistler[45] as well as Rabelo and Van Es[46]. Daniel and Zingaro[47] also reported the S_N2 displacement of the p-tolylsulfonyl group at C-6 position of a pyranose ring with selenocyanate ion.

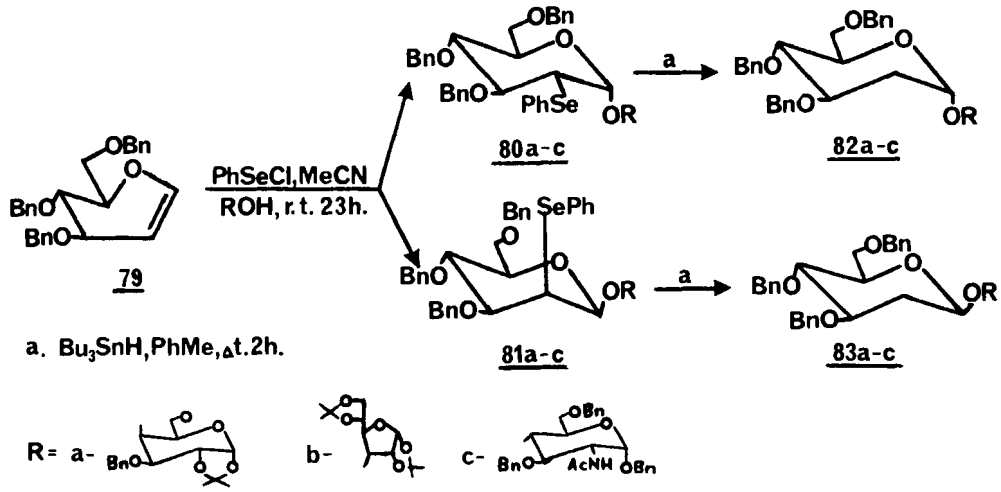
Introduction of the arylselene residue into the sugar moiety has been accomplished by addition of phenylselenyl halides to olefins.[48-49] These methods are based on the Sharpless[49] procedure of addition of ArSeX to olefin bonds. Another example of ArSeX additions to olefins

involves cyclization through reactions with internal nucleophiles has been reported.[50-55]

A second method of introduction of the arylselene residue into the sugar ring is opening of the oxirane ring of sugars with PhSeH which has been reported mainly by David and coworkers.[56-60]

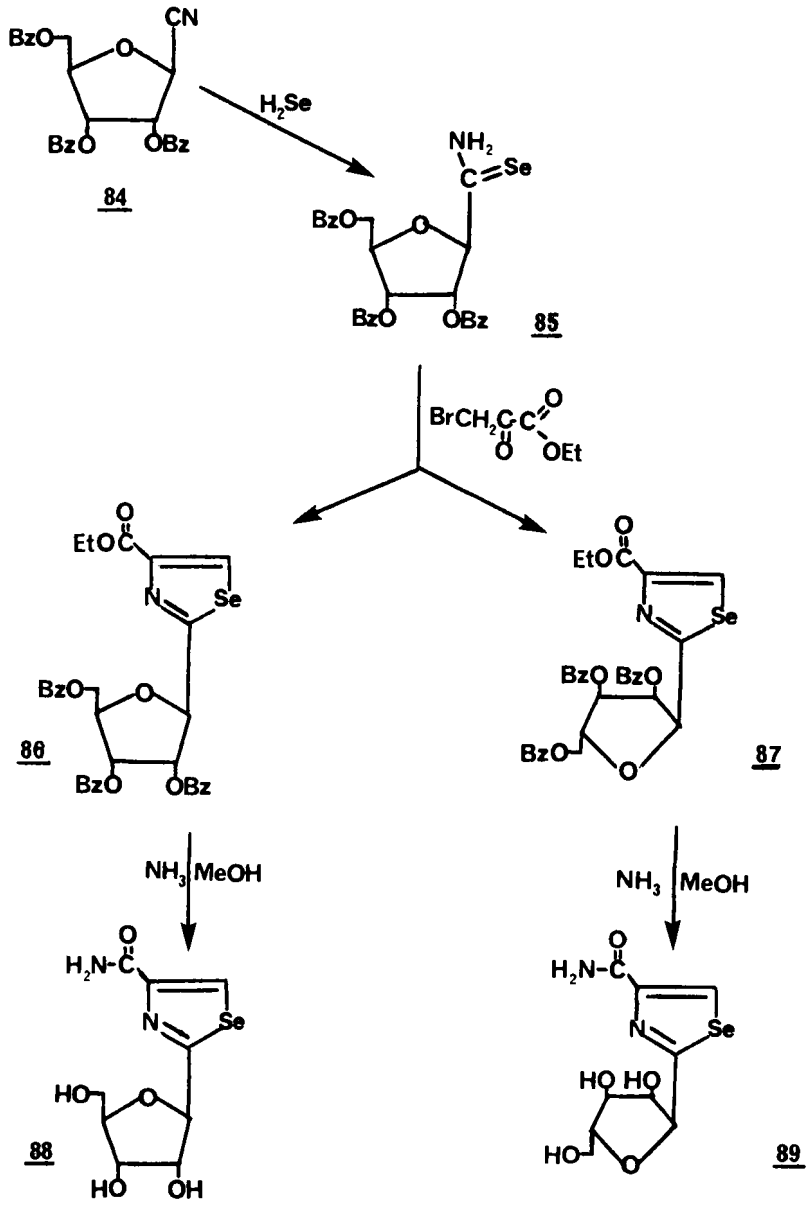
These methods of conversions of epoxides into phenyl selenides which were intermediates to unsaturated derivatives of sugars are based on the Sharpless and Lauer method of synthesis of allylic alcohols from epoxides.[61-64]

An interesting synthetic approach to 2'-deoxy-disaccharides (82a-c) an (83a-c) has recently been published by Sinaÿ and coworkers.[65] This reaction proceeds via stereoselective glycosyloxyselenation of 3,4,6-tri-O-benzyl D-glucal (79) followed by reductive removal of the phenylseleno group with tributyltin hydride in excellent yield 90-95%.



The first introduction of selenazole as a base in nucleosides was reported recently by Srivastava and Robins.[66] The reaction sequence starts with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-1-carbonitrile (84). Treatment of (84) with liquid hydrogen selenide in the presence of 4-(dimethylamino)-pyridine as catalyst afforded (85) which on condensation with ethyl bromopyruvate provided ethyl 2-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-selenazole-4-carboxylate as a mixture of α and β

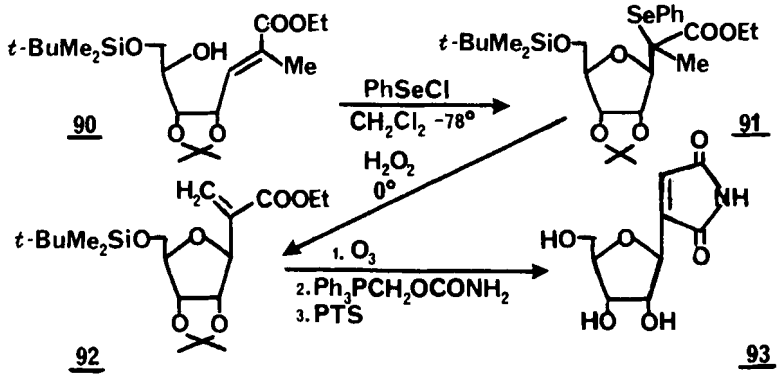
(86 and 87) anomers, which were readily separated by silica gel column chromatography. Treatment of (86) and (87) with methanolic ammonia



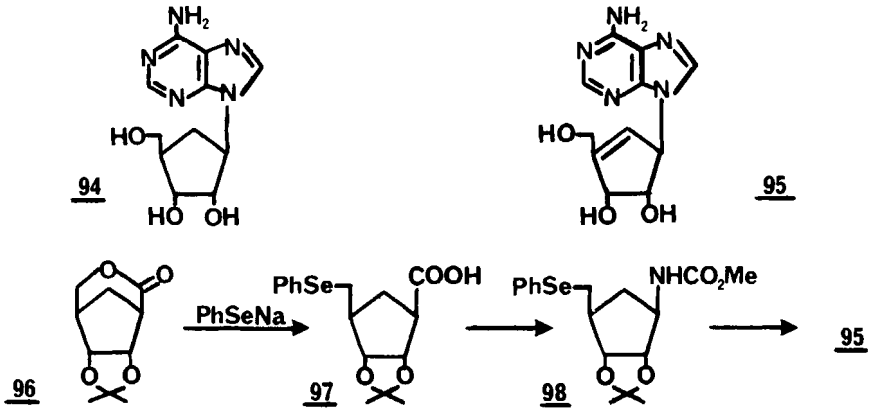
provided the corresponding nucleoside analogs (88) and (89), respectively, in moderate yields. Phosphorylation of (88) with trichloropyrophosphopyridinium chloride, provided the appropriate nucleotide, 2-β-D-

ribofuranosylselenazole-4-carboxamide 5'-phosphate, in 42% yield. This nucleotide was a target compound as a potential inhibitor of inosine monophosphate (IMP) dehydrogenase, in analogy with the previous observations on corresponding thiazole congener.

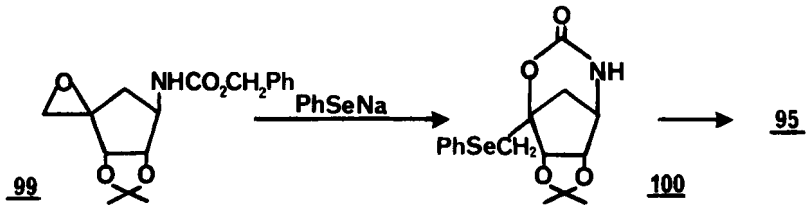
Recently a selenium intermediate was used to facilitate stereoselective ring closure of a ribose derivative (91) as a key intermediate in a new approach to the C-nucleoside showdomycin (93).[67]



An interesting synthetic approach to carbocyclic nucleosides aristeromycin (94) and neplanocin A (95) starts from the corresponding lactone (96) and proceeds via selenide (97).

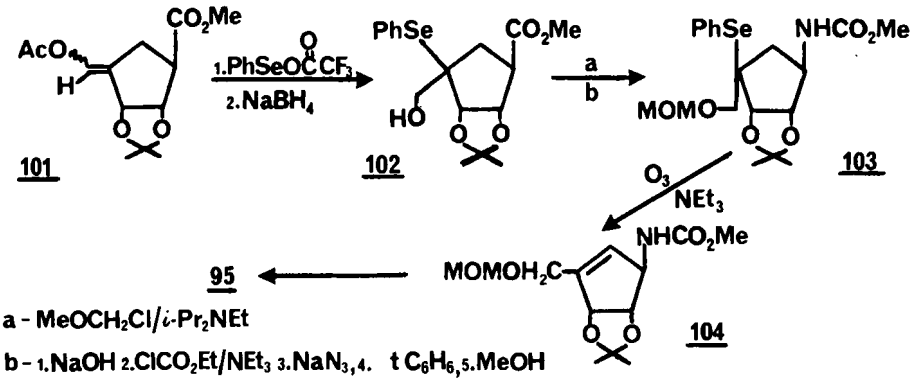


It is noteworthy that similar ring opening of epoxide (99) with phenyl selenoate ion generated in situ from diphenyl selenide and sodium borohydride in N,N-dimethylformamide solution afforded cyclic carbamate (100) a key intermediate to (95).



The formation of the cyclic carbamate (100) is only possible between the β-epoxide and β-benzyl carbamate groups in a cis relation as has been reported by these authors.[68]

A third route to (95) starts from (101) and proceeds via selenides (102) and (103), which treatment with ozone in triethylamine, which effectively promotes syn elimination, afforded the key-intermediate (104) to (95).



3. ANTITUMOR ACTIVITY OF SELENONUCLEOSIDE ANALOGS

The well known antitumor activity of 6-thioguanine[69-71] as well as the better therapeutic index and comparable antitumor inhibition for the selenium cogener, i.e., 6-selenoguanine[8] prompted synthesis of 6-selenoguanosine[11,13] as a potentially much more effective antitumor agent. A comparative investigation (thio vs seleno) showed[71,72] that selenoguanine and selenoguanosine inhibit the growth of Sarcoma 180 Ascites cells more effectively than the corresponding thionucleosides. However, according to the report of Chu and Davidson[19] β-2'-deoxy-6-selenoguanosine was found to have an activity approximately equal to 6-thio congener, while α-anomer was much less active than corresponding α-2'-deoxy-6-thioguanosine. This was confirmed by the report of Milne

and Townsend[17-18] who also observed that alkylation of both anomers at the exocyclic selenium atom appears to cause a marked decrease in antitumor activity.

Moreover, 6-alkylselenopurine ribonucleosides[20] displayed no antitumor activity and were more toxic than the corresponding guanosine analogs. It is also noteworthy[72] that 6-methylselenoguanosine is completely inactive as an inhibitor, whereas the 6-selenoguanosine-platinum (II) complex[73] exhibits antitumor activity against L 1210 cells in mice and on in vitro systems. Interestingly, the seleno-guanine-platinum (II) complex[73] in mice was retained longer than the parent compound, selenoguanine, because the selenoguanine-platinum (II) complex very slowly, released selenoguanine into the blood, accord-ing to the observation of these authors.[73]

On the other hand, 6-selenoguanosine and 6-alkylselenoguanosine derivatives were found to be the most active compounds in the 6-seleno-inosine[20] and 6-alkylguanosine[18] groups. Also the 8-substituted seleno cyclic GMP derivatives[23,25] showed some antitumor activity against murine leukemic cells (L5178Y) in vitro and in vivo. It was also shown that cyclic nucleotides[23] are more active than the cor-responding nucleosides. However, none of the tested compounds inhibits cell growth at very low concentrations. It is noteworthy that the analog of 8-isoselenouronium-cGMP-hydrobromide (29) is a very active inhibitor (98% inhibition)[25]. This fact illustrates its potential as an antitumor agent. Also the cytotoxicity of 6-selenopurine arabino-side and 6-alkylseleno-derivatives has been reported[31], however, the cytotoxicity of the above analogs was below 50% inhibition.

The in vitro antitumor activity of 2-β-D-ribofuranosyl-selenazole-4-carboxamide (88) as well as its 5'-phosphate in comparison with the corresponding thiazole congeners were found to be more active toward P388 and L1210 cells in culture and also effective against Lewis lung carcinoma in mice.

4. CONCLUSION

The preceding review of the preparative chemistry of selenonucleo-sides is a continuation of a previous report on the chemistry of seleno-sugars.[1] Introduction of selenium into purines and pyrimidines as well as into the sugar moiety, causes many changes either in the biolog-

ical activity (mainly antitumor activity) or the chemical reactivity. Instability of the selenoxo group in many derivatives practically eliminates the possibility of application of these compounds as potential anticancer agents. However, there is one report[66] on the synthesis of the first selenazolenucleoside analogs and preliminary results of the biological activity indicates that this class of compounds will be a subject of research and investigation in the near future.

ACKNOWLEDGMENT

I wish to thank Dr. James R. Daniel, Department of Food and Nutrition, Purdue University, West Lafayette, Indiana 47907 U.S.A. for helpful discussion and reading this manuscript.

REFERENCES

1. Part I. Carbohydrates Containing Selenium. Z. J. Witczak and R. L. Whistler, Heterocycles, 1982, 19, 1719.
2. Present address for correspondence: Department of Biochemistry, Purdue University, West Lafayette, IN 47907 U.S.A.
3. S. Hanessian and H. G. Pernet, Adv. Carbohydr. Chem. Biochem., 1976, 33, 111; G. D. Daves and Cheng C. C., Prog. Med. Chem., 1976, 13, 303.
4. R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York 1970; R. J. Suhadolnik, "Nucleoside as Biological Probes," Wiley-Intersicence, New York 1979.
5. J. Southon and W. Pfleiderer, Chem. Biol. Pteridines, Proc. 5th Internat. Symposium, 1975, 783, Chem. Abs., 1976, 84, 189481y.
6. J. A. May and L. B. Townsend, J. Carbohydr. Nucleosides, Nucleotides, 1975, 2, 271; ibid; 1975, 2, 371.
7. H. G. Mautner, J. Am. Chem. Soc., 1956, 78; 5292.
8. H. G. Mautner, S. H. Chu, J. J. Jaffe and A. Sartorelli, J. Med. Chem., 1963, 6, 36.
9. J. J. Jaffe and H. Mautner, Cancer Res., 1958, 18, 938.
10. J. J. Jaffe and H. G. Mautner, Cancer Res., 1960, 20, 381.
11. L. B. Townsend and G. H. Milne, J. Heterocycl. Chem., 1970, 7, 753.
12. G. H. Milne and L. B. Townsend, J. Heterocycl. Chem., 1971, 8, 379.

13. S. H. Chu, J. Med. Chem., 1971, 14, 254.
14. C. Y. Shiue and S. H. Chu "Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques". Eds. L. B. Townsend and R. S. Tipson, Wiley-Interscience, New York, 1978, Vol. 2, p. 673.
15. Y. A. Beltagy, W. Waugh and A. J. Repta, J. Pharm. Sci., 1980, 69, 1168.
16. A. J. Repta and Y. A. Beltagy, J. Pharm. Sci., 1981, 70, 634.
17. G. H. Milne and L. B. Townsend, Biochim. Biophys. Acta, 1972, 269, 344.
18. G. H. Milne and L. B. Townsend, J. Med. Chem., 1974, 17, 263.
19. S. H. Chu and D. D. Davidson, J. Med. Chem., 1972, 15, 1088.
20. G. H. Milne and L. B. Townsend, J. Chem. Soc. Perkin. Tr. I., 1972, 2677.
21. D. S. Wise and L. B. Townsend, J. Heterocycl. Chem., 1972, 9, 1461.
22. D. S. Wise and L. B. Townsend "Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques." Eds. L. B. Townsend and R. S. Tipson, Wiley-Intersciency, New York, 1978, Vol. 1, p. 413.
23. S. H. Chu, C. Y. Shiue and M. Y. Chu, J. Med. Chem., 1974, 17, 406.
24. C. Y. Shiue and S. H. Chu, J. Heterocycl. Chem., 1975, 12, 493.
25. S. H. Chu, C. Y. Shiue and M. Y. Chu, J. Med. Chem., 1975, 18, 559.
26. D. A. Saelinger, J. L. Hoffman and K. P. McConnell, J. Mol. Biol., 1972, 69, 9.
27. J. L. Hoffman and K. P. McConnell, Biochim. Biophys. Acta, 1974, 366, 109.
28. A. J. Wittwer, Fed. Proc., 1981, 40, 1645.
29. C. S. Chen, T. N. Wen, and H. M. Tuan, Biochim. Biophys. Acta, 1982, 699, 92.
30. C. S. Chen, and T. C. Stadtman, Proc. Natl. Acad. Sci. U.S.A., 1980, 77, 1403.
31. S. H. Chu, C. Y. Shiue and M. Y. Chu, J. Pharm. Sci., 1975, 64, 1343.
32. C. Y. Shiue and S. H. Chu, J. Org. Chem., 1975, 40, 2971.
33. C. Y. Shiue and S. H. Chu, J. Chem. Soc. Chem. Comm., 1975, 319.

34. C. Y. Shiue and S. H. Chu, J. Org. Chem., 1976, 41, 1847.
35. G. H. Milne and L. B. Townsend, J. Heterocycl. Chem., 1976, 13, 745.
36. G. H. Milne and L. B. Townsend, J. Carbohyd. Nucleosides, Nucleotides, 1976, 3, 177.
37. D. S. Wise and L. B. Townsend, Tetrahedron Letters, 1977, 755.
38. D. S. Wise and L. B. Townsend, J. Chem. Soc. Chem. Comm., 1979, 271.
39. D. S. Wise, G. H. Milne and L. B. Townsend, Heterocycles, 1981, 15, 345.
40. S. D. Clayton, J. A. Montgomery, and J. A. Secrist III, submitted for publication.
41. H. Takaku, T. Namoto and K. Kimura, Chem. Lett., 1981, 1221.
42. N. Zylber, J. Zylber and A. Gaudemer, J. Chem. Soc. Chem. Comm., 1978, 1084.
43. M. Sekine, and T. Hata, Chem. Lett., 1979, 801.
44. C. Boullais, N. Zylber, J. Zylber, J. Guilhem and A. Gaudemer, Tetrahedron, 1983, 39, 759.
45. T. Van Es and R. L. Whistler, Tetrahedron, 1971, 23, 2849.
46. J. J. Rabelo and T. Van Es, Carbohydr. Res., 1973, 30, 381.
47. J. R. Daniel and R. A. Zingaro, Carbohydr. Res., 1978, 64, 69.
48. K. Mori, Tetrahedron Letters, 1976, 1609.
49. S. Current and K. B. Sharpless, Tetrahedron Letters, 1978, 5078.
50. K. C. Nicolau and Z. Lysenko, Tetrahedron Letters, 1977, 1259.
51. K. C. Nicolau and Z. Lysenko, J. Am. Chem. Soc., 1977, 99, 3186.
52. D. L. J. Clive, G. Chittattu and C. K. Wong, Can. J. Chem., 1977, 55, 3894.
53. D. L. J. Clive, G. Chittattu, N. J. Curtis, W. A. Kiel and C. K. Wong, J. Chem. Soc. Chem. Comm., 1977, 725.
54. D. L. J. Clive, G. Chittattu and C. K. Wong, J. Chem. Soc. Chem. Comm., 1978, 441.
55. D. L. J. Clive, C. K. Wong, W. A. Kiel and S. M. Menchen, J. Chem. Soc. Chem. Comm., 1978, 379.
56. S. David, A Lubineau and J. M. Vatele, J. Chem. Soc. Chem. Comm., 1975, 701.
57. S. David, A. Lubineau and J. M. Vatele, J. Chem. Soc. Perkin Tr. I., 1976, 1831.
58. K. Torssel and M. P. Tyagi, Acta Chem. Scand. B., 1977, 31, 297.

59. S. David and A. Lubineau, Nov. J. Chem., 1977, 1, 375.
60. Y. Nishimura, H. Umezawa, and S. Umezawa, Tetrahedron Letters, 1981, 77.
61. K. B. Sharpless and R. F. Lauer, J. Am. Chem. Soc., 1972, 94, 7154.
62. K. B. Sharpless and R. F. Lauer, J. Org. Chem., 1972, 37, 3973.
63. K. B. Sharpless, M. W. Young and R. F. Lauer, J. Am. Chem. Soc., 1972, 94, 154; ibid., 1973, 95, 2697.
64. K. B. Sharpless, M. W. Young and F. R. Lauer, Tetrahedron Letters, 1973, 1979.
65. G. Jaurand, J. M. Beau, and P. Sinaÿ, J. Chem. Soc. Chem. Comm., 1981, 572.
66. P. Srivastava and R. K. Robins, J. Med. Chem., 1983, 26, 445.
67. P. D. Kane and J. Mann, J. Chem. Soc. Chem. Comm., 1983, 224.
68. H. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, J. Am. Chem. Soc., 1983, 105, 4049.
69. G. A. LePage and N. Howard, Cancer Res., 1963, 23, 622.
70. G. A. LePage, Cancer Res., 1960, 20, 403.
71. G. W. Crabtree, E. M. Scholar, S. H. Chu and R. E. Parks Jr., Biochem. Pharmacol., 1973, 22, 155.
72. A. F. Ross, K. G. Agrawal. S. H. Chu and R. E. Parks Jr., Biochem. Pharmacol., 1973, 22, 141.
73. M. Maeda, N. Abiko and T. Sasaki, J. Med. Chem., 1981, 24, 167.

Received June 13, 1983