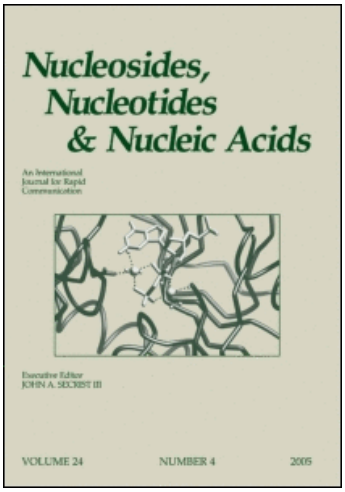

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Sodium Thiosulfate and Potassium Selenosulfate as Reagents to Prepare Thio-and Selenopurine Nucleosides

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SODIUM THIOSULFATE AND POTASSIUM SELENOSULFATE AS REAGENTS TO PREPARE THIO- AND SELENOPURINE NUCLEOSIDES

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Abstract - The synthesis of 6-thio- and 6-seleno- derivatives of inosine and guanosine as well as the 8-thio- and 8-seleno- derivatives of adenosine, inosine and guanosine were prepared from a reaction of the corresponding 6-chloro- and 8-bromo- derivatives with sodium thiosulfate and potassium selenosulfate, respectively.

INTRODUCTION

6-Thio- and 6-selenopurine ribonucleosides have been prepared by a number of methods. 6-Thiopurine ribosides have been synthesized by the treatment of 6-chloropurine ribosides with methanolic sodium hydrogen sulfide[1], treatment of the protected (acetyl or benzoyl) 6-oxo-nucleosides with phosphorus pentasulfide in pyridine[2], or by a reaction of the 6-chloronucleosides with thiourea in ethanol.[3] In addition, 6-methoxyadenosine has been treated with hydrogen sulfide-pyridine-water, to afford 6-thioinosine in 77% yield. Treatment of adenosine, under these conditions or under forcing conditions, afforded 6-thioinosine in low yield.[4]

The first 6-selenopurine ribonucleoside was synthesized by the treatment of 6-chloropurine riboside with methanolic sodium hydrogen selenide.[5] 6-Selenoguanosine was prepared from the corresponding 2-amino-6-chloropurine riboside and methanolic sodium hydrogen selenide[6] or by treatment with selenourea in ethanol.[7] Heating adenosine or 2-aminoadenosine with an excess of hydrogen selenide in pyridine-water in a sealed tube has afforded the corresponding 6-seleno-nucleosides, 6-selenoinosine and 6-selenoguanosine.[8]

The synthesis of 8-thiopurine ribonucleosides has been accomplished by a reaction of the 8-bromo- derivatives with thiourea in ethanol,[9] while the 8-selenonucleosides have been prepared by the treatment of the 8-bromo-compounds with ethanolic sodium hydrogen selenide[10] or selenourea in ethanol.[11]

It has been reported that sodium thiosulfate, sodium selenosulfate or potassium selenosulfate react with nitrobenzyl chlorides or bromides to give nitrobenzyl mercaptans or selenides.[14a,b] Following this work it was later shown[12] that 6-chloropurine and other heterocyclic halides react with sodium thiosulfate pentahydrate to give 6-mercaptopurine and the corresponding thiols in good yield. However, no direct conversion of 6-chloro-, 8-bromopurine nucleosides, or other halonucleosides to thio- or selenonucleosides with inorganic thiosulfates and selenosulfates have been reported.

We have been very involved for several years, in the synthesis of thio- and selenonucleosides[13] and cyclic selenopurine nucleosides.[11b] We have now investigated the use of these salts[14] as an alternative route for the preparation of 6-thio-, 8-thio- and the corresponding selenonucleosides by treatment of the corresponding 6-chloro- and 8-bromopurine nucleosides with these inorganic salts.

DISCUSSION

When a 6-chloronucleoside was heated at reflux with 1 eq of sodium thiosulfate pentahydrate in 75% aqueous ethanol, the conversion

to a 6-thio- derivative was essentially complete within 24 hr. The reaction was found to be quite facile. If an excess of sodium thiosulfate pentahydrate was used in the reaction, the reaction time was reduced to 6 hr. This prompted us to use an excess of reagent in all subsequent reactions. Reaction of 6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purines with an excess of sodium thiosulfate pentahydrate effected a concurrent deacetylation to afford the unprotected 6-thiopurine nucleosides in somewhat lesser yield than the corresponding reactions with unblocked nucleosides.

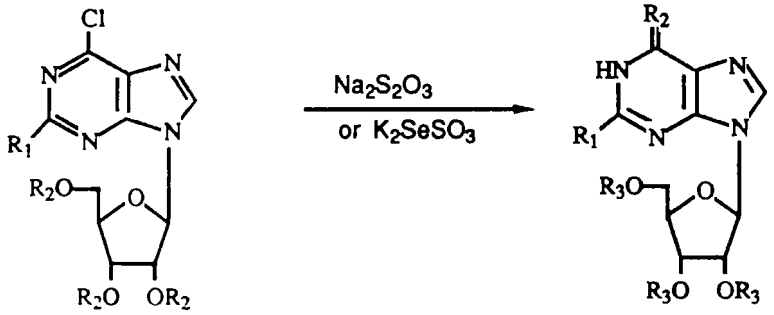
To prepare selenonucleosides, we choose to use potassium selenosulfate[14] to react with the 6-chloropurine nucleosides rather than the sodium selenosulfate since the potassium salt was more soluble in a mixture of water-ethanol. The reactions with potassium selenosulfate were carried out under argon to avoid both a decomposition of the salt and the possible formation of a di-selenide derivative. We found that reactions to prepare the 6-seleno-derivatives required less time than the preparation of the corresponding 6-thio-derivatives. This was probably due to the greater nucleophilicity of the selenium anion.

It was necessary to heat the 8-bromonucleosides with an excess of sodium thiosulfate pentahydrate or potassium selenosulfate for longer periods of time (12-18 hr) and at a higher temperature. This was presumably due to the lower reactivity of the halo group at the C-8 position of the purine ring system. In each case the selenonucleosides were recrystallized from an acetate buffer (0.01 M, pH 4.5) in the presence of ascorbic acid[21] to prevent a conversion of the 6-seleno- and 8-selenonucleosides to the corresponding diselenides in aqueous solution.

Thus, it appears that the reaction of halo purine ribosides with thiosulfates or selenosulfates is general in nature. This method effects a deacylation and therefore should not be used to obtain blocked nucleosides.

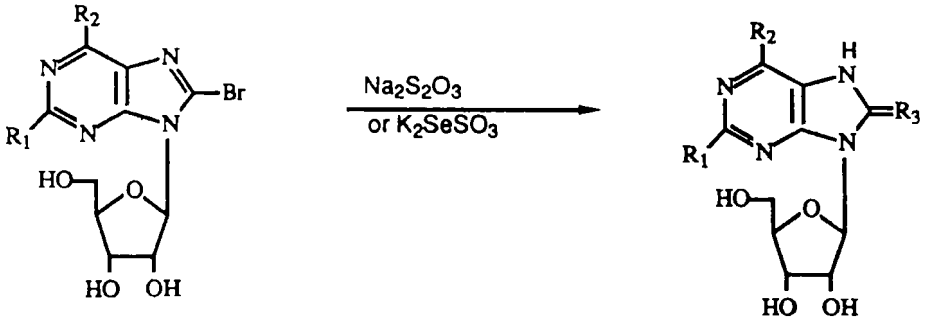
EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP 270SY spectrometer using DMSO-d_6 as solvent. UV spectra were recorded on a Hewlett-



1a. R_1 = H, R_2 = S, R_3 = H
1b. R_1 = H, R_2 = Se, R_3 = H
1c. R_1 = H, R_2 = S, R_3 = Ac

2a. R_1 = NH_2, R_2 = S, R_3 = H
2b. R_1 = NH_2, R_2 = Se, R_3 = H
2c. R_1 = NH_2, R_2 = S, R_3 = H



3. R_1 = H, R_2 = NH_2

4. R_1 = NH_2, R_2 = OH

5. R_1 = H, R_2 = OH

6a. R_1 = H, R_2 = NH_2, R_3 = S
6b. R_1 = H, R_2 = NH_2, R_3 = Se

7a. R_1 = NH_2, R_2 = OH, R_3 = S
7b. R_1 = NH_2, R_2 = OH, R_3 = Se

8a. R_1 = H, R_2 = OH, R_3 = S
8b. R_1 = H, R_2 = OH, R_3 = Se

TABLE I

Thio- and Selenonucleosides from Thiosulfate and Selenosulfate Reactions

Substrate	Product	Yield %	M.p. °C	Lit. M.p. °C	Ref.
6-chloropurine riboside[15]	6-thioinosine	83	225-227	208 210	1, 2
	6-selenoinosine	54	210-212	212-214	5
6-chloroguanosine[6c,16]	6-thioguanosine	78	230-232	224-227	2
	6-selenoguanosine	65	206-208	206-208	6c
8-bromoadenosine[17]	8-thioadenosine	69	175 dec.	171-173	9
				164-166	10
	8-selenoadenosine	60	156-158	125-127	11b
8-bromoguanosine[18]	8-thioguanosine	72	215-220	>220 dec	9
	8-selenoguanosine	56	212-215	210 dec.	11a
8-bromoinosine[19]	8-thioinosine	60	248	244-245	20
	8-selenoinosine	51	228-230	232-234	22
2',3',5'-tri-O-acetyl 6-chloropurine riboside[15]	6-thioinosine	65	223-225	208-210	11
2',3',5'-tri-O-acetyl 6-chloroguanosine[6c,16]	6-thioguanosine	72	228-230	224-227	2

Packard 8450 A Uv/Vis spectrophotometer. Analtech silica gel GHLF plates were used for tlc in the following systems: dichloromethane-methanol = 8:2 (v:v) (A), dichloromethane-methanol = 9:1 (v:v) (B), and 2-propanol-water-conc. ammonium hydroxide = 7:2:1 (v:v:v) (C). The yields and other data relating to the synthesis of thio- and selenonucleosides are given in Table 1.

General Procedure for Preparing 6-, and 8-Thiopurine Nucleosides

a) 6-Thionucleosides

From unprotected nucleosides. 6-Chloronucleoside (1 mmol) and sodium thiosulfate pentahydrate (4 eq) in a mixture of water (30 mL) and ethanol (30 mL) was heated at reflux for 6 hr. The solvent was then evaporated to dryness under vacuum. The resulting residue was treated with cold water (10 mL) (5°C) and dried at room temperature in vacuo over P_2O_5. Tlc in systems B and C shows single spot.

From protected nucleosides. The 2',3',5'-tri-O-acetyl-6-chloro- nucleoside (1 mmol) was dissolved in 10 mL of hot ethanol. To this mixture was added dropwise, sodium thiosulfate pentahydrate (4 eq) in 30 mL of water. The solution was stirred and heated at reflux for 6 hr. The solvent was evaporated to dryness in vacuum and the residue was treated with cold water (5°C) and dried in vacuo over P_2O_5. Tlc in systems B and C showed that the product was the unprotected 6-thionucleoside by a comparison with an authentic sample.

b) 8-Thionucleosides

8-Bromonucleoside (1 mmol) and sodium thiosulfate pentahydrate (5 eq) in a mixture of butanol (40 mL), ethanol (20 mL), and water (10 mL) were heated on an oil bath (125-130°C) for 18 hr. The solvent was then evaporated to dryness under vacuum. The resulting residue was washed with cold water (10 mL, 5°C) and then dried at room temperature in vacuo over P_2O_5.

General Procedure for Preparing 6-, and 8-Selenopurine Nucleosides

a) 6-Selenonucleosides

6-Chloronucleoside (1 mmol) and potassium selenosulfate[14] (3 eq) in a mixture of water (15 mL) and ethanol (30 mL) was heated at reflux under argon for 3 hr. After cooling, the precipitated metallic selenium was removed by filtration and the solvent was evaporated to dryness under vacuum. The residue and ascorbic acid (0.5 g) were dissolved in 10 mL of acetate buffer (0.01 M, pH 4.5) by heating. The hot solution was filtered through a glass microfibre filter (Whatman G) and the filtrate was allowed to stand at 4°C for 15 hr. A yellow precipitate was collected by filtration and washed with ice-cold water (10 mL). The solid was dried at room temperature in vacuo over P_2O_5. Tlc in systems A and C showed single spots.

b) 8-Selenonucleosides

8-Bromonucleoside (1 mmol) and potassium selenosulfate[14] (4 eq) in a mixture of n-butanol (40 mL), ethanol (20 mL), and water (10 mL) was heated on an oil bath (125-130°C) under argon for 12 hr. After cooling, the precipitated metallic selenium was removed by filtration and the solvent was evaporated to dryness under vacuum. The residue and ascorbic acid (0.5 g) were dissolved in 10 mL of acetate buffer (0.01 M, pH 4.5) by heating. The hot solution was filtered through a glass microfibre filter (Whatman G) and allowed to stand at 4°C for 15 hr. The yellow precipitate was collected by filtration and washed with ice-cold water (10 mL). The solid was dried at room temperature in vacuo over P_2O_5. Tlc in system A and C shows single spot.

8-Selenoinosine (5b)

8-Selenoinosine was prepared from 8-bromoinosine[19] and potassium selenosulfate as described above. Yield 48%: m.p. 228-2300 (lit.[22] 232-234°C); uv (MeOH) [λ_{max} in nm ($\varepsilon \times 10^{-3}$)] 275 (20.7); ^{1}H NMR (DMSO-d_6): δ 6.46 (1H, H-1', d, $J_{1',2'}$ = 5.5 Hz), 8.12 (1H, H-

2,s); tlc (C) R_f = 0.65; Anal. Calcd. for $C_{10}H_{12}N_4O_5Se$: C, 34.59; H, 3.48; N, 16.14. Found: C, 34.34; H, 3.66; N, 16.07.

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22. 8-Selenoinosine has been made in our laboratory independently by two different ways: first from treatment of 8-bromoinosine with selenourea in 2-butanol-ethanol solution and second by deamination of 8-selenoadenosine; m.p. 232-234°C.

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