Novel Synthesis of Anhydronucleosides *via* the 2′,3′-*O*-Sulfinate of Purine Nucleosides as Intermediates

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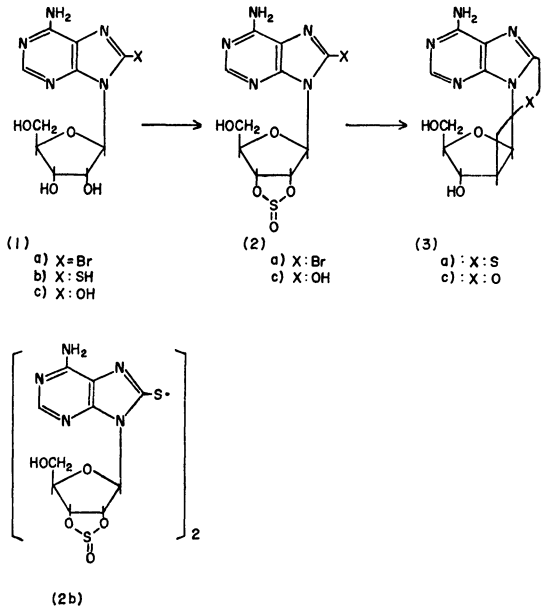
The synthesis of 8,2′-*O*-anhydro(9-β-D-arabinofuranosyl)-8-hydroxyadenine (**3c**) and 8,2′-*S*-anhydro(9-β-D-arabinofuranosyl)-8-mercaptoadenine (**3a**) is described. The active intermediates, 2′,3′-*O*-sulfinyl 8-bromoadenosine (**2a**), 2′,3′-*O*-sulfinyl-8-hydroxyadenosine (**2c**), and 2′,3′-*O*-sulfinyl-8-bromoguanosine (**2d**), were prepared from the corresponding nucleosides (**1a**, **1c** or **1d**) by successive treatment with thionyl chloride in the presence of pyridine in acetonitrile and with water. The anhydronucleosides, **3a** and **3c**, were formed in good yields by heating the intermediates (**2a** or **2c**) in *n*-butanol in the presence of thiourea or in *N*,*N*-dimethylformamide in the presence of sodium acetate. All attempts at the cyclization of Compound **2d** failed. The reaction product of 8-mercaptoadenosine (**1b**) with thionyl chloride was identified as the bis(2′,3′-*O*-sulfinyl adenosin-8-yl) disulfide (**2b**), which could not be transformed to Compound **3a**.

Anhydronucleosides are important analogues of natural nucleosides. 8,2′-Anhydronucleosides are key intermediates in the synthesis of many biologically active compounds and have provided new routes for the nucleotides.[1,2] Anhydronucleosides have been synthesized, by several procedures, from natural or unnatural nucleosides *via* the corresponding activated intermediates, such as tosyl,[3] triisopropylbenzene sulfonyl[4] or carbonyl derivatives,[5] but most of these methods are tedious.

The present authors[6] have previously reported that anhydropyrimidinenucleosides can be conveniently prepared in high yields *via* the corresponding 2′,3′-*O*-sulfinates as intermediates. In the present paper we wish to describe a simple and efficient method for the anhydropurine nucleosides.

Results and Discussion

Ogilvie[5] prepared 8,2′-thioanhydro(9-β-D-arabinofuranosyl)-8-mercaptoadenine by heating 2′,3′-*O*-carbonyl-8-bromoadenosine in the presence of thiourea in *n*-butanol. The essential step in the preparation of anhydronucleosides is the introduction of a good leaving group to the 2′ and 3′-positions in the ribose moiety of nucleosides, as is outlined in Scheme 1. In order to establish a convenient method applicable for large-scale preparation, a cyclic sulfinyl group[6] was used as the leaving froup; it was considered to be more active than the cyclic carbonyl group.



Scheme 1.

Thionyl chloride was allowed to react with 8-bromoadenosine (**1a**) in the presence of pyridine in acetonitrile at the temperature of 5 °C for 3 hr. Paper chromatography showed the presence of a single spot with an R_f-value of 0.91 other than that of the **1a** meterial (0.71). The reaction product was isolated in a 64% yield by pouring the reaction mixture into ice water and by then adjusting the pH of the resulting solution to pH 2.5 with sodium bicarbonate. The structure of the acylation product was identified as 2′,3′-*O*-sulfinyl-8-bromoadenosine (**2a**), which was negative to a periodate-benzidine test[7] and which gave ultraviolet spectra similar to those of **1a**. The alkaline hydrolysis of **2a** eliminated the cyclic sulfinyl group to give the **1a** material. The **2a** product had a broad band due to S=O stretching and three sharp bands associated with the five-membered cyclic sulfinyl group at 1201, 1205, and 1210 cm^{-1} in the infrared spectrum.[8] The elemental analysis of **2a** agreed with the proposed structure.

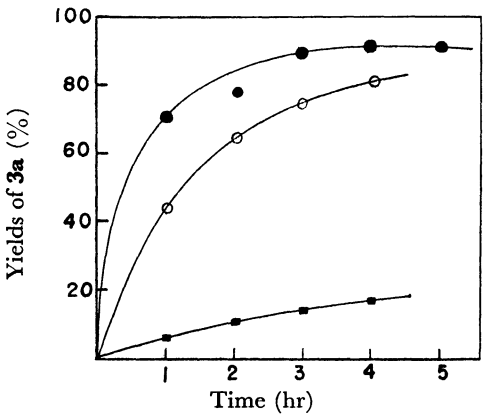


Fig. 1. Effect of reaction temperature of the preparation of **3a**.
Experimental conditions: 2′,3′-*O*-sulfinyl-8-bromoadenosine 1 mmol, thiourea 4 mmol, *n*-butanol 100 ml at 119 °C (●), 100 °C (○), 70 °C (■).

Table 1. Properties of nucleoside derivatives

Compound	Mp °C (d)[a]	R_f, PPC		UV-Spectrum λ_{max}, nm
		Solv. A	Solv. B	
1a	196	0.08	0.67	263
2a	146—148	—	0.90	260
3a	212—214	0.12	0.61	276
4a	184—188	0.38	0.49	257
1b	171—173	0.14	0.68	221, 243, 308
2b	142	—	0.91	281
1c	237—238	0.25	0.31	264, 284
2c	85— 92	—	0.82	264, 284
3c	202—202.5	0.45	0.25	260
4c	190—191	0.53	0.18	223, 248, 308
5c	252	0.19	0.45	257
1d	180	0.39	0.29	260
2d	175—177	—	0.85	258

a) d: decompose.

In *n*-butanol, **2a** was stable at the temperature of 80 °C in the presence of thiourea but was transformed to **3a** at an elevated temperature (Fig. 1). When **2a** was refluxed in *n*-butanol in the presence of thiourea, the reaction went essentially to completion after 4 hr to form a 8,2′-thioanhydro-linkage. The reaction product was isolated in a 70% yield and was identified as 8,2′-*S*-anhydro(9-β-D-arabinofuranosyl)-8-mercaptoadenine (**3a**) by a comparison of the physical properties with those of an authentic sample.[5] Compound **3a** was easily converted to 2′-deoxyadenosine (**4a**) by reducing it with Raney-Ni.

The treatment of 8-mercaptoadenosine (**1b**) with thionyl chloride under the same conditions as **1a** gave a single product, with an R_f-value of 0.9, by paper chromatography. Compound **2b** had a λ-maximum at 281 nm in the aqueous solution at pH 2.0, and its ultraviolet spectrum differed from that of the **1b** material (307 nm). Though the **2b** product had a broad band due to S=O stretching at 1000—1050 cm^{-1} and three fairly sharp bands associated with a five-membered cyclic sulfinyl group at 1200, 1205, and 1210 cm^{-1}, the specific absorption peak due to the SH group could not be found at 2550 cm^{-1} in the infrared spectrum. These facts show that the structure of the **2b** product is the bis(2′,3′-*O*-sulfinyladenosin-8-yl) disulfide. The elemental analysis of **2b** agreed with the proposed structure. All attempts at the cyclization of **2b** failed.

8-hydroxyadenosine (**1c**) was allowed to react with thionyl chloride under the same conditions as **1a** to give 2′,3′-*O*-sulfinyl-8-hydroxyadenosine (**2c**) as the single product, as shown by paper chromatography. By heating **2c** in *N*,*N*-dimethylformamide at 115 °C for 1 hr in the presence of sodium acetate, 8,2′-*O*-anhydro(9-β-D-arabinofuranosyl)-8-hydroxyadenosine (**3c**) was obtained in a 44.3% yield. The physicochemical properties of **3c** were in good agreement with those of an authentic sample.[9] By treatment with hydrogen sulfide in pyridine, **3c** was easily converted to 9-β-D-arabinofuranosyl-8-mercaptoadenine (**4c**), which was then transformed to 9-β-D-arabinofuranosyladenine (**5c**) by treating it with Raney-Ni. The physical properties of **4c** and **5c** are listed in Table 1; they are identical with those of authentic samples. Though the 2′,3′-*O*-sulfinyl-8-bromoguanosine (**2d**), much like **2a**, was formed quantitatively by treating 8-bromoguanosine (**1d**) with thionyl chloride, Compound **2d** could not be transformed to the corresponding anhydronucleoside, presumably because Compound **2d** is conformationally the "Syn" form.

The above method of synthesizing the anhydropurine nucleosides is superior to those of Ikehara[9] and Ogilvie[5] with respect to the yield and the simplicity of the procedure.

Experimental

The ultraviolet spectra were recorded on a Hitachi EPS-3T spectrophotometer, and the infrared spectra, on a Hitachi EPI-G2. The paper chromatography of the reaction products was carried out by the ascending technique on Toyo-Roshi No. 51 paper (40 cm×40 cm) using the following solvent system: Solv. A; *n*-butanol–acetic acid–water (4: 1: 5); Solv. B; 2-propanol–saturated ammonium sulfate–1 M-sodium acetate (2: 79: 19). The UV and chromatographic properties are shown in Table 1.

2′,3′-O-Sulfinyl-8-bromoadenosine (2a). Freshly distilled thionyl chloride (21.6 ml, 300 mmol) and pyridine (24 ml, 300 mmol) were placed in 100 ml of acetonitrile, after which the mixture was set aside at the temperature of 5 °C. To the solution we then added 8-bromoadenosine (34.7 g, 100 mmol), and the mixture was stirred at 5 °C for 3 hr. Then, 300 ml of water was mixed with the reaction mixture to destroy the reactant under vigorous stirring. Paper chromatography showed the presence of a single spot with an R_f value of 0.9 (solvent B); an aqueous extract of it showed an absorption maximum at 260 nm (pH 1.0). The resulting reaction mixture was adjusted to pH 2.5 with sodium bicarbonate and was then kept in the refrigerator overnight. The white precipitates thus obtained were collected by filtration, washed with water, and dried to yield 24.4 g (64%) of 2′,3′-*O*-sulfinyl-8-bromoadenosine; mp 146—148 °C (dec.).

Found: C, 31.6; H, 2.5; N, 18.0, Br, 19.5; S, 8.1%. Calcd for $C_{10}H_{10}N_5O_5S \cdot Br$: C, 30.6; N, 2.5, H, 17.8; Br, 20.4; S, 8.2%.

2′,3′-O-Sulfinyl-8-bromoguanosine (2d). Into a mixed solution of thionyl chloride (21.6 ml), pyridine (24 ml), and acetonitrile (100 ml), we vigorously stirred 8-bromoguanosine (100 mmol); the reaction solution was then maintained for

3 hr at 5 °C. A 300 ml portion of water was then added to the reaction mixture, and the pH of the resulting solution was adjusted to 2.5 with sodium bicarbonate. The white precipitates thus obtained were collected, washed with water, and then dried to yield 25.4 g (64.3%) of 2′,3′-*O*-sulfinyl-8-bromoguanosine. Mp 175—177 °C (dec.); R_f 0.85 (solv. B), λ_{max} 258 nm (pH 2.0).

Found: C, 30.8; N, 17.1; S, 7.89%. Calcd for $C_{10}H_{10}N_5O_6Br$: C, 29.4; N, 17.1; S, 7.8%.

*2′,3′-O-Sulfinyl-8-hydroxyadenosine (**2c**).* Into a mixed solution of thionyl chloride (3.6 ml, 50 mmol), pyridine (2.4 ml, 30 mmol), and acetonitrile (30 ml), we vigorously stirred 8-hydroxyadenosine (2.8 g, 10 mmol), after which the reaction solution was maintained for 2 hr at 0 °C. A 250 ml portion of acetonitrile was added to the resulting mixture, and the solid thus precipitated was collected by filtration, washed with acetonitrile and twice with ether, and then dried to yield 2.84 g (85.7%) of 2′,3′-*O*-sulfinyl-8-hydroxyadenosine hydrochloride. Mp 85—92 °C (dec.); R_f 0.82 (solv. B).

Found: C, 32.5; H, 3.2; N, 17.3; S, 7.87; Cl, 10.14%. Calcd for $C_{10}H_{11}O_6N_5S\cdot HCl$: C, 32.8; H, 3.3; N, 19.2; S, 8.74; Cl, 9.71%.

*Bis(2′,3′-O-sulfinyladenosin-8-yl) Disulfide (**2b**).* Into a mixed solution of thionyl chloride (10.8 ml, 150 mmol), pyridine (12 ml, 150 mmol), and acetonitrile (50 ml), we vigorously stirred 8-mercaptoadenosine (15 g, 50 mmol), after which the reaction solution was maintained for 3 hr at 0 °C. A 300 ml portion of water was added to the reaction mixture under vigorous stirring to destroy the reactant. The resulting aqueous solution was adjusted to pH 2.5 with sodium bicarbonate and was then kept in the refrigerator overnight. The precipitates were collected by the filtration and then washed with water and dried to yield 12.6 g of bis(2,3′-*O*-sulfinyladenosin-8-yl) disulfide. Mp 142 °C (dec.); R_f 0.9 (solv. B), λ_{max} 281 nm (pH 2.0).

*8,2′-S-Anhydro(9-β-D-arabinofuranosyl)-8-mercaptoadenine (**3a**).* 2′,3′-*O*-Sulfinyl-8-bromoadenosine (21 g, 50 mmol) and thiourea (14 g, 200 mmol) were dissolved in 5 l of *n*-butanol, and the solution was refluxed for 4 hr. After drying the reaction mixture *in vacuo*, the residual product was dissolved in hot water and then cooled. The solid thus precipitated was collected by filtration and then washed with cold water and dried to give 10.2 g (70%) of 8,2′-*S*-anhydro(9-β-D-arabinofuranosyl)-8-mercaptoadenine. Mp 212—214 °C (dec.); $[\alpha]_D^{20}$ −178.1° (*c*, 0.5, H_2O) λ_{max} 276 nm (pH 2.0), R_f 0.12 (solv. A), 0.61 (solv. B). Found: C, 41.0; H, 4.2; N, 23.2; S, 9.67%. Calcd for $C_{10}H_{11}N_5O_3S\cdot 1/2H_2O$: C, 41.4; H, 4.1; N, 24.1; S, 11.0%.

*8,2′-O-Anhydro(9-β-D-arabinofuranosyl)-8-hydroxyadenine (**3c**).* 2′,3′-*O*-sulfinyl-8-hydroxyadenosine hydrochloride (5.5 g, 15 mmol) and sodium acetate (2.8 g, 45 mmol) were heated in *N,N*-dimethylformamide (1500 ml) for 45 min at 115 °C. After the reaction mixture had been dried *in vacuo*, the residual product was dissolved in 1 l of water; then the aqueous solution was submitted to electrodialysis with an ion-exchange membrane. The resulting solution was evaporated *in vacuo*, and white precipitates were collected, washed with water, and dried to yield 1.32 g (44.3%) of 8,2′-*O*-anhydro(9-β-D-arabinofuranosyl)-8-hydroxyadenine monohydrate. Mp 202—202.5 °C (dec.); λ_{max} 260 nm (pH 2.0).

Found: C, 42.90; H, 4.38; N, 24.7%. Calcd for $C_{10}H_{11}O_4N_5\cdot H_2O$: C, 42.40; H, 4.59; N, 24.73%.

*2′-Deoxyadenosine (**4a**).* 8,2′-*S*-Anhydro(9-β-D-arabinofuranosyl)-8-mercaptoadenine (4.6 g, 16.9 mmol) and Raney-Ni (30 g, Ni-content 50%) were mixed with 400 ml of water. The mixture was then refluxed for 2 hr. The nickel was removed by filtration, and the filtrate and washings (hot water) were combined and evaporated *in vacuo* to about 40 ml. A 100 ml portion of methanol was added to the concentrated solution, and the solid thus precipitated was collected by filtration, washed with water, and dried to give 2.88 g (67%) of 2′-deoxyadenosine. Mp 184—188 °C (dec.); R_f 0.49 (solv. B), λ_{max} 257 nm (pH 2), λ_{min} 232 nm (pH 2).

Found: C, 47.83; H, 5.11; N, 26.73%. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.18; N, 26.89%.

*8-Mercapto-9-β-D-arabinofuranosyl Adenine (**4c**).* 8-Mercapto-9-β-D-arabinofuranosyl adenine was prepared by Ikehara's method.[9] 8,2′-*O*-Anhydro(9-β-D-arabinofuranosyl)-8-hydroxyadenine monohydrate (1.1 g, 4 mmol) was dissolved in pyridine (40 ml) and liquid H_2S (obtained by cooling with dry-ice–acetone, 40 g). The mixture was sealed in a steel tube and heated at 100 °C for 16 hr. The tube was then cooled with dry-ice and N_2 gas was bubbled through to remove the H_2S completely. The pyridine was removed by the distillation *in vacuo*, and the residual product was crystallized from water to yield 1.0 g (78.4%) of 8-mercapto-9-β-D-arabinofuranosyl adenine monohydrate. Mp 190—191 °C (dec.); λ_{max} 223, 248, 208 nm (pH 2).

Found: C, 37.81; H, 4.75; N, 21.98; S, 9.95%. Calcd for $C_{10}H_{13}N_5O_4S\cdot H_2O$: C, 37.85; H, 4.73; N, 22.08; S, 10.09%.

*9-β-D-Arabinofuranosyl Adenine[9] (**5c**).* 8-Mercapto-9-β-D-arabinofuranosyl adenine monohydrate (4.5 g, 15 mmol) dissolved in 750 ml of water, and Raney-Ni (7.5 g) was added. The mixture was refluxed for 3 hr. The nickel was removed by filtration, and the filtrate and washings (hot water) were combined and concentrated *in vacuo*. The solid thus precipitated was collected by filtration, washed with water, and dried to yield 4.05 g (90%) of 9-β-D-arabinofuranosyl adenine monohydrate. Mp 252 °C (dec.); λ_{max} 257 nm (pH 2.0), R_f 0.19 (solv. A), 0.45 (solv. B).

Found: C, 42.15; H, 5.33; N, 24.28%. Calcd for $C_{10}H_{13}N_5O_4\cdot H_2O$: C, 42.10; H, 5.23; N, 24.56%.

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