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Synthesis of 2′-thioadenosine*

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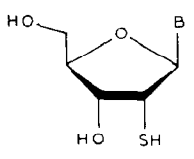
ABSTRACT

Reaction between 6-*N*-benzoyl-9-[3,5-*O*-(1,1,3,3-tetra-isopropyldisiloxane-1,3-diyl)-2-*O*-trifluoromethanesulfonyl-β-D-arabinofuranosyl]adenine (**12a**), prepared from 9-(β-D-arabinofuranosyl)adenine, and 9-(4-methoxyphenyl)xanthene-9-thiol (AXT, **7b**) in the presence of N^1,N^1,N^3,N^3-tetramethylguanidine, followed by treatment with tetraethylammonium fluoride in acetonitrile and then with methanolic ammonia, gave the 2′-*S*-[9-(4-methoxyphenyl)xanthen-9-yl] derivative (**13**) of the title compound (**1c**) in good yield. Compound **1c** was obtained, also in good yield, when **13** was heated at 70° with pyrrole in acetic acid solution. The preparation of 9-(2-thio-β-D-arabinofuranosyl)adenine (**5**) by a similar route is also described.

INTRODUCTION

Nucleoside analogues with functional group or stereochemical modifications in their sugar residues are potential antibiotic, anti-tumour, and anti-viral agents[1]. An



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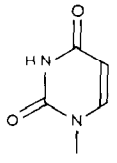
1b B = 3a
1c B = 4



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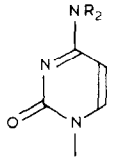

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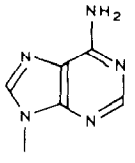
3b R = Me



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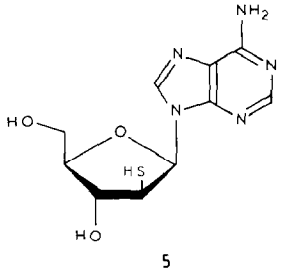

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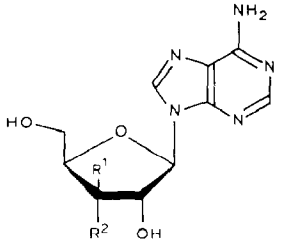

6a R^1 = H, R^2 = SH
6b R^1 = SH, R^2 = H

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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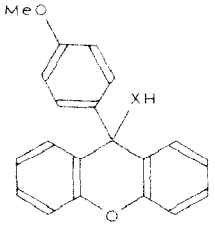
obvious way to modify a ribonucleoside is to replace HO-2′ by a thiol group. Such 2′-thioribonucleosides (**1**) should, in addition to being potentially biologically active, be readily convertible into the corresponding 2′-deoxyribonucleosides by reductive desulfuration[2].

Prior to our recent study[3], the only fully characterised 2′-thioribonucleoside described in the literature was the uridine derivative[2] **1a**. Although the preparation of the cytidine derivative **1b** has also been reported[4], the product described was not fully characterised and the n.m.r. data obtained left the structural assignment open to doubt. We have[3] prepared and characterised 2′-thiouridine (**1a**), and the hydrochlorides of 2′-thiocytidine (**1b**) and 4,4-di-*N*-methyl-2′-thiocytidine (**1**, B = **3b**). However, to the best of our knowledge, no synthesis of a 2′-thioribonucleoside (**1**) with a purine aglycon has previously been reported. While the preparation of three isomers (**5**, **6a**, and **6b**) of 2′-thioadenosine (**1c**) has been reported[5,6], all previous attempts[5,7] to prepare **1c** have failed. We now describe the synthesis of **1c** and the corresponding *arabino* isomer[6] (**5**) by what we believe will prove to be a method of general application.

RESULTS AND DISCUSSION

Very recently, we described[8] the preparation of 9-(4-methoxyphenyl)xanthene-9-thiol (AXT, **7b**) and its use in the conversion of 5′-chloro-5′-deoxyribonucleosides (**8a**) into the corresponding 5′-thionucleosides (**8b**) in satisfactory yields. AXT[8] (**7b**) is a stable crystalline solid which may easily be prepared in high yield (see Experimental) by passing hydrogen sulphide through a cooled solution of 9-(4-methoxyphenyl)xanthen-9-ol[9] (**7a**) and dichloroacetic acid in dichloromethane. The conversion of adenosine (**9**) into 2′-thioadenosine (**1c**), using AXT (**7b**) in the key thiation step, is indicated in the sequence **9** → **13** → **1c**.

3′,5′-*O*-(1,1,3,3-Tetra-isopropyldisiloxane-1,3-diyl)adenosine (**10**), which was prepared (88%) by reacting adenosine (**9**) with 1,3-dichloro-1,1,3,3-tetra-isopropyldisiloxane[10] in pyridine *N*,*N*-dimethylformamide, was converted into the corresponding 9-(β-D-arabinofuranosyl)adenine derivative (**11**; ~58%) in two steps (see Experimental) essentially following the procedure of Hansske *et al.*[11]. Compound **11** was then converted into its 6-*N*-benzoyl derivative **12** (93%) by treatment first with an excess of



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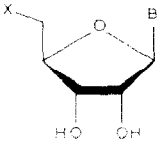
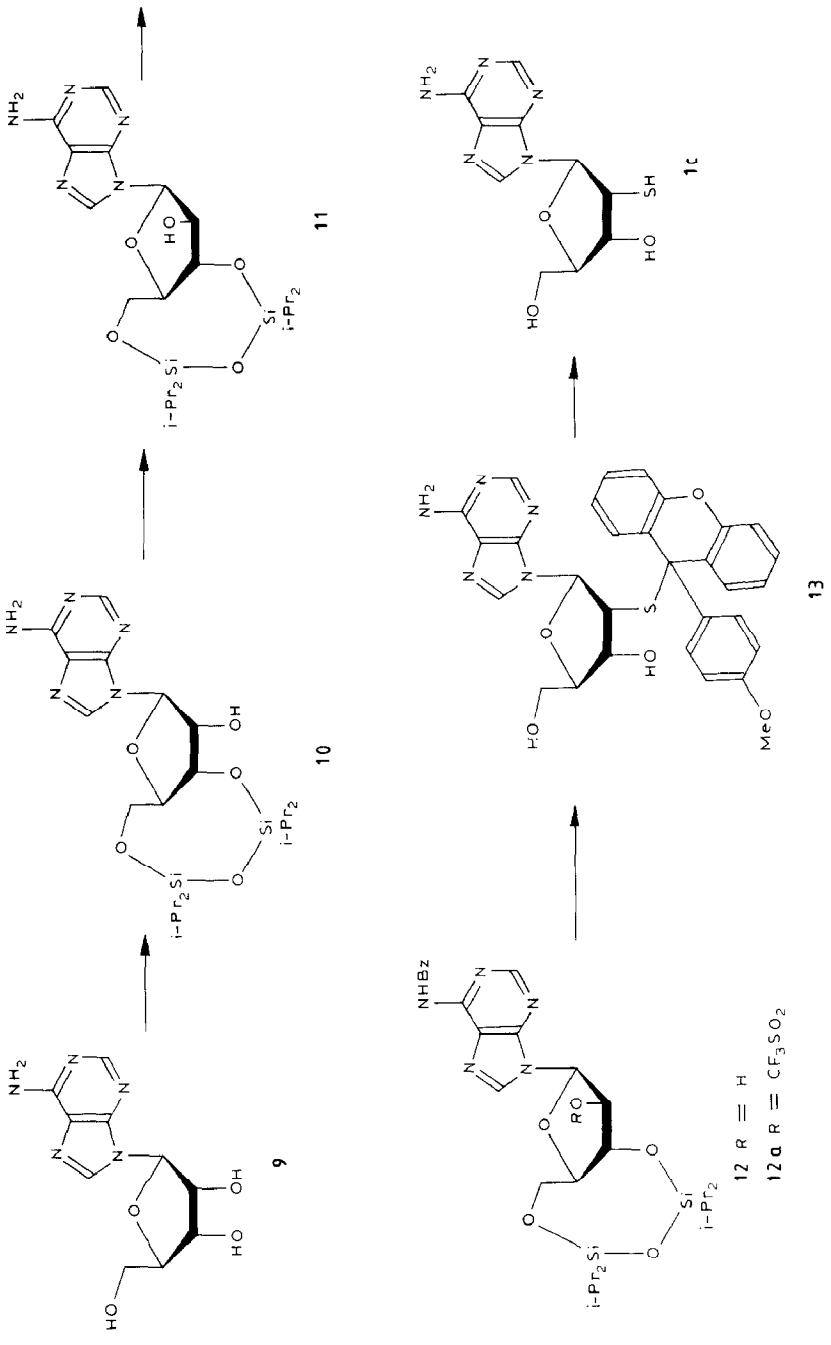
7b X = S

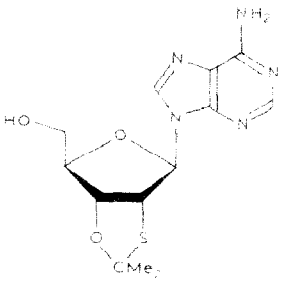


8a X = Cl
8b X = SH


NH2
HO
OH
i-Pr2Si
Si
i-Pr2
9
10
11
1c
SH
NHBz
RO
12 R = H
12a R = CF3SO2
13
MeC

benzoyl chloride in pyridine and then with sodium methoxide. The required 2′-triflate (**12a**; >80%) was obtained by treating **12** with 1.5 mol of trifluoromethanesulfonic anhydride in pyridine–dichloromethane.

The key thiation step was effected by allowing the triflate ester **12a** to react with ~2.0 mol of AXT[5] (**7b**) and ~1.5 mol of N^1,N^1,N^3,N^3-tetramethylguanidine in methyl sulfoxide solution in an atmosphere of nitrogen at room temperature for 2 h. The tetra-isopropyldisiloxanyl and benzoyl groups were removed from the resulting protected 2′-thioether by treatment with tetraethylammonium fluoride in acetonitrile[12] followed by methanolic ammonia. After chromatography, 2′-*S*-[9-(4-methoxyphenyl)xanthen-9-yl]-2′-thioadenosine (**13**) was obtained and isolated as a crystalline solid (~76%, based on **12a**). Finally, the 9-(4-methoxyphenyl)xanthen-9-yl protecting group was removed by heating **13** with a tenfold excess of pyrrole in acetic acid solution[13], under nitrogen, at 70° for 1 h. 2′-Thioadenosine (**1c**) was thereby obtained and isolated as a crystalline solid (78%). This reaction does not proceed in the absence of pyrrole[13] which appears to be an efficient carbocation scavenger.



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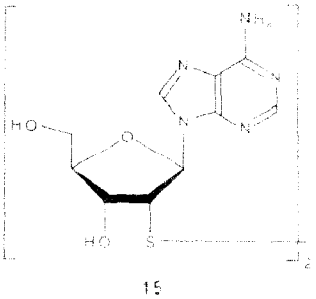

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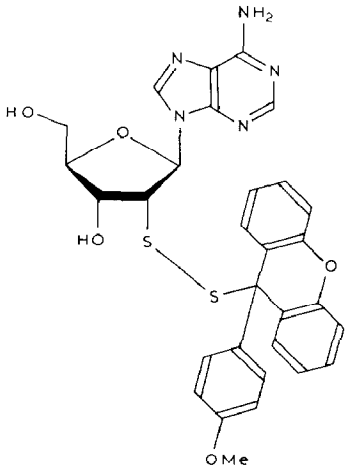
The structure of 2′-thioadenosine (**1c**) was assigned on the basis of elemental analysis, n.m.r. (especially ^{13}C) data (Table I), its reaction with 2,2-dimethoxypropane, and the fact that it readily undergoes iodine-promoted oxidative dimerisation. The resonance signal at 44.64 p.p.m. in the ^{13}C-n.m.r. spectrum of **1c** is assigned to C-2′; its chemical shift is closely similar to those of the corresponding signals observed[5] in the spectra of 2′-thiouridine (**1a**, 44.87 p.p.m.) and the hydrochlorides of 2′-thiocytidine (**1b**, 45.95 p.p.m.) and 4,4-di-*N*-methyl-2′-thiocytidine [**1** (B = **3b**), 45.72 p.p.m.]. Reaction of **1c** with a large excess of 2,2-dimethoxypropane in the presence of toluene-4-sulphonic acid monohydrate in acetonitrile at room temperature gave its 2′-*S*,3′-*O*-isopropylidene derivative **14** which was isolated as a crystalline solid (68%). This clearly demonstrates the *cis*-relationship of HS-2′ and HO-3′. Finally, reaction of **1c** with ~0.5 mol of iodine in ethanol–pyridine–water (20:1:3 v:v) at room temperature gave[5] the dimeric disulfide **15** in good yield. Compound **15** was readily distinguishable from **1c** in two t.l.c. systems (see Experimental) and by the n.m.r. data (Table I). The resonance signal at 54.94 p.p.m. in the ^{13}C-n.m.r. spectrum of **15** is assigned to C-2′, like the corresponding resonance signals observed[5] at 55.52, 57.48, and 57.56 p.p.m. in the

^{13}C-n.m.r. spectra of the dimers of **1a**, **1b**, and **1** (B = **3b**), respectively, it is more than 10 p.p.m. downfield from the C-2′ resonance signal observed in the spectrum of its monomeric precursor (**1c**). T.l.c. and n.m.r. evidence indicated that the 2′-thioadenosine (**1c**) obtained was not detectably contaminated with the disulfide (**15**).



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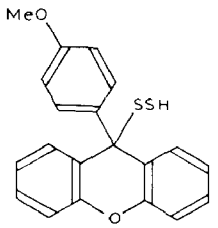


17

TABLE I

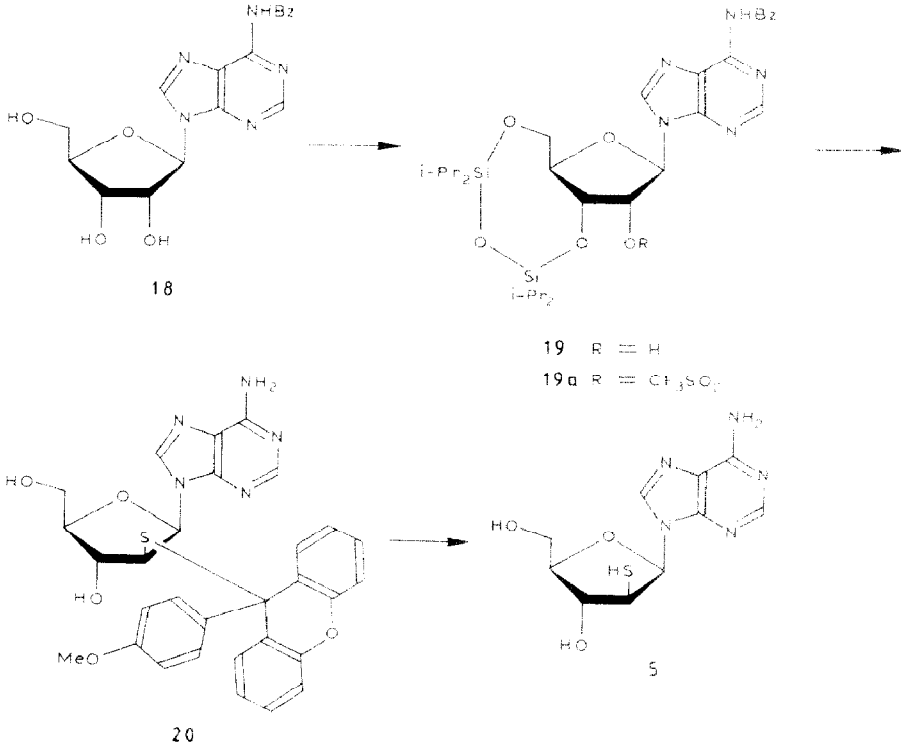
N.m.r. data[a] (δ in p.p.m., J in Hz) for 2′-thioadenosine (**1c**) and derivatives

Compound	*H-1′* (J)	*H-2′* (J)	*H-3′* (J)	*C-2′*
13	5.85 d (9.8)	3.80 dd (4.3, 9.8)	3.3	51.62
1c	5.97 d (9.2)	4.09 dd (4.9, 9.2)	4.53 d (5.0)	44.64
14	6.04 d (7.8)	4.81 dd (5.1, 7.7)	5.01 d (5.2)	54.53
15	6.14 d (8.4)	4.32 dd (5.2, 8.4)	4.11	54.94
16	6.01 d (8.2)	2.75 dd (5.3, 8.1)	3.95	55.70

[a] Obtained for solutions in $(CD_3)_2SO$ except in the case of **1c** when CD_3CO_2D was used.

The above reaction between the triflate **12a** and AXT (**7b**) proceeded rapidly in methyl sulfoxide in the presence of the strong base N^1,N^1,N^3,N^3-tetramethylguanidine and in the absence of atmospheric oxygen to give, following treatment with tetraethylammonium fluoride in acetonitrile and methanolic ammonia, **13** as the sole detectable nucleoside product. However, when triethylamine was used as the base and atmospheric oxygen was not excluded, a relatively slow reaction ensued and only ~14% of **13** was obtained together with ~35% of the disulphide **16**. The structure of **16** was based on its elemental analysis, n.m.r. data (Table I), and on its ready conversion by sulfur extrusion (see below) into **13**. A noteworthy feature of the ^{1}H-n.m.r. spectrum of **16** is the exceptional shielding of H-2′, presumably by the 9-(4-methoxyphenyl)xan-

then-9-yl group. In the ^{1}H-n.m.r. spectrum of **13** (Table I), in which C-2′ is linked to the 9-(4-methoxyphenyl)xanthen-9-yl group by only one sulfur atom, H-3′ rather than H-2′ is particularly shielded. It is further relevant to note that the chemical shift of the C-2′ resonance (55.70 p.p.m.) in the ^{13}C-n.m.r. spectrum of **16** is closely similar to that of the corresponding resonance (54.94 p.p.m.) in the spectrum of the symmetrical disulfide **15**. Disulfides corresponding to **16** were also obtained[8] as by-products in the reactions between 5′-chloro-5′-deoxyribonucleosides (**8a**), AXT (**7b**), and *N*′,*N*′,*N*′,*N*′-tetramethylguanidine. It is possible that the conjugate base of AXT undergoes oxidative dimerisation in the presence of atmospheric oxygen and then loses one 9-(4-methoxyphenyl)xanthen-9-yl residue to give the conjugate base of **17**. As the latter species could reasonably be expected to be a good nucleophile, substantial quantities of the disulfide **16** are then likely to result, provided that the reaction between the triflate **12a** and the conjugate base of AXT (**7b**) proceeds only slowly. Finally, when the disulfide **16** was heated with a slight excess of triphenylphosphine in glacial acetic acid[8] at 50° for 2 h, 2′-*S*-[9-(4-methoxyphenyl)xanthen-9-yl]-2′-thioadenosine (**13**, 75%) was obtained.



Essentially the same procedure was then used to prepare the previously described[9] 9-(2-thio-β-D-arabinofuranosyl)adenine (**5**). 6-*N*-Benzoyladenosine (**18**) was first converted into its 1,1,3,3-tetra-isopropyldisiloxane-1,3-diyl derivative **19** (~79%). Treatment of **19** with trifluoromethanesulfonic anhydride in pyridine – dichloromethane solution gave the triflate **19a** (~89%) which was then subjected to the three-step procedure used above in the conversion of **12a** → **13** to give

9-{2-*S*-[9-(4-methoxyphenyl)xanthen-9-yl]-2-thio-β-D-arabinofuranosyl}adenine (**20**; 26% overall yield for the five steps starting from **18**). Removal of the 9-(4-methoxyphenyl)xanthen-9-yl protecting group was effected, as described above, to give **5** (72%) as a crystalline solid.

We believe that the present study, together with the previous study[8] relating to the preparation of 5′-thioribonucleosides (**8b**), establishes AXT (**7b**) as the reagent of choice for the conversion of sulfonate esters of nucleosides and related deoxyhalogenonucleosides (such as **8a**) into the corresponding thiols. Indeed, it is reasonable to conclude that AXT is likely to prove to be of general value in the synthesis of thiols.

EXPERIMENTAL

General methods. — Unless otherwise stated, ^{1}H- (360.1 MHz) and ^{13}C-n.m.r. (90.6 MHz) spectra (internal Me_4Si) were obtained with a Bruker AM 360 spectrometer. Short-column chromatography was carried out on silica gel H (Merck), and t.l.c. on silica gel 60 F_{254} plates (Merck) which were developed in $CHCl_3$–MeOH mixtures *A*, 97:3; *B*, 19:1; *C*, 9:1; and *D*, 4:1; *E*, CH_2Cl_2–EtOAc (4:1); and *F*, *n*-BuOH–AcOH–H_2O (5:3:2). Acetonitrile, pyridine, and triethylamine were dried by heating with calcium hydride, under reflux, and then distilled. *N*,*N*-Dimethylformamide, methyl sulfoxide, and N^1,N^1,N^3,N^3-tetramethylguanidine were dried by heating with calcium hydride, at ~80°, and then distilled under reduced pressure. Dichloromethane was dried by heating with phosphorus pentaoxide, under reflux, and then distilled. Ether was dried over sodium wire.

9-(4-Methoxyphenyl)xanthen-9-ol (**7a**). — To a mixture of magnesium turnings (14.7 g, 0.60 g atom) and dry ether (100 mL) was added a portion (~6 mL) of a solution of 4-bromoanisole (75 mL, 0.60 mol) in dry ether (100 mL) together with methyl iodide (a few drops). The stirred mixture was heated gently and, when the Grignard reaction began, cooled to ~15°. The remainder of the ethereal 4-bromoanisole was then added during ~20 min, at such a rate to ensure gentle boiling. The mixture was then heated, under gentle reflux, for 1 h, and cooled. Xanthen-9-one (53.5 g, 0.27 mol) was added in portions during 5–10 min, and more dry ether (100 mL) was added. The mixture was heated, under reflux, for 2 h, and the product was collected by filtration, washed well with ether, powdered, and added in portions with swirling to conc. hydrochloric acid (300 mL), cooled in an ice-bath. The resulting dark-red solution was added dropwise, with vigorous stirring, to ice–water (2 L), and the mixture obtained was extracted with dichloromethane (2 L). The extract was washed successively with saturated aqueous sodium hydrogen carbonate (3 × 1.5 L) and water (2 × 1 L), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallised from cyclohexane to give **7a** (68.0 g, 82%), m.p. 167.5–168.5° (from ether); lit.[9] m.p. 146–147°. ^{13}C-N.m.r. data ($CDCl_3$): δ 55.14, 70.13, 113.21, 116.33, 123.48, 127.35, 128.88, 128.93, 140.38, 149.64, 158.17.

9-(4-Methoxyphenyl)xanthene-9-thiol (*AXT*, **7b**). — Hydrogen sulfide was bubbled through a cooled (ice–water bath), stirred, dry solution of dichloroacetic acid (20.8

mL, 0.25 mol) in dichloromethane (500 mL) while a solution of **7a** (38.6 g, 0.127 mol) in dry dichloromethane (600 mL) was added dropwise during 1 h. After hydrogen sulfide had been bubbled through the mixture for a further 15 min, the products were washed with saturated aqueous sodium hydrogen carbonate (2 × 1 L) and then water (2 × 1 L), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallised from cyclohexane to give **7b** (36.0 g, 88.5%), m.p. 118–120°. ^{13}C-N.m.r. data ($CDCl_3$): δ 51.31, 55.19, 113.18, 116.38, 123.41, 128.30, 129.06, 129.43, 130.22, 138.20, 149.58, 158.45 (Found: C, 74.8; H, 4.9. $C_{20}H_{16}O_2S$ calc.: C, 75.0; H, 5.0%).

3′,5′-O-(1,1,3,3-Tetra-isopropyldisiloxane-1,3-diyl)adenosine (**10**). — 1,3-Dichloro-1,1,3,3-tetra-isopropyldisiloxane[10] (17 mL, 53.1 mmol) was added dropwise during 30 min to a rapidly stirred suspension of adenosine (13.2 g, 49.4 mmol) in dry *N,N*-dimethylformamide (145 mL) and pyridine (40 mL) at room temperature. After a further 1 h, triethylamine (20 mL) and methanol (25 mL) were added, and the mixture was concentrated under reduced pressure at <40° (bath). The residue was partitioned between dichloromethane (300 mL) and saturated aqueous sodium hydrogen carbonate (300 mL), the aqueous layer was back-extracted with dichloromethane (100 mL), and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Toluene was evaporated several times from the residue under reduced pressure. Silica gel chromatography (hexane–chloroform, 1:1; and then chloroform–ethanol, 100:0 → 95:5) of the residual glass gave **10** as a colourless solid (22.2 g, ~88%); R_f 0.31 (solvent *B*). Recrystallisation from acetonitrile gave fine needles, m.p. 97–99°; lit.[13] m.p. 98–99.5°. ^1H-N.m.r. data: ^1H[(CD_3)$_2$SO], δ 1.04 (m, 28 H), 3.93 (dd, 1 H, *J* 2.5 and 12.5 Hz), 4.01 (m, 1 H), 4.07 (dd, 1 H, *J* 3.2 and 12.6 Hz), 4.51 (m, 1 H), 4.80 (dd, 1 H, *J* 5.1 and 8.5 Hz), 5.64 (d, 1 H, *J* 4.5 Hz), 5.88 (d, 1 H, *J* 0.9 Hz), 7.34 (bs, 2 H), 8.07 (s, 1 H), 8.21 (s, 1 H); ^{13}C ($CDCl_3$): δ 12.59, 12.81, 13.06, 13.33, 16.91, 16.99, 17.01, 17.10, 17.32, 17.36, 17.38, 17.48, 61.44, 70.44, 75.12, 82.03, 89.90, 120.29, 139.24, 149.00, 152.98, 155.87.

9-[3,5-O-(1,1,3,3-Tetra-isopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]adenine (**11**). — Dry pyridine (28.7 mL, 0.355 mol) was added to a vigorously stirred suspension of chromium(VI) oxide (17.4 g, 0.174 mol) in dry dichloromethane (406 mL) at room temperature. After 20 min, acetic anhydride (16.4 mL, 0.174 mol) was added and, after 8 min, the mixture was cooled to 20° and a warm solution of 3′,5′-*O*-(1,1,3,3-tetra-isopropyldisiloxane-1,3-diyl)adenosine (22.2 g, 43.5 mmol) in dry dichloromethane (115 mL) was added in portions during 3 min. After a further 8–9 min, the mixture was poured rapidly with swirling into ethyl acetate (2 L). The resulting brown suspension was transferred to a column (diam. 9 cm) of silica gel (3.5 cm depth) in ethyl acetate, which was eluted with ethyl acetate. The eluate was concentrated under reduced pressure, and toluene was evaporated several times from the residue. A solution of sodium borohydride (2.29 g, 60.5 mmol) in water (14 mL) was added dropwise over a period of 5 min to a stirred solution of the resulting material in ethanol (158 mL) at 0°. After 30 min, ethyl acetate (550 mL) was added, the mixture was washed with brine (170 mL, 2 × 80 mL), and the combined aqueous layers were extracted with ethyl acetate (200 mL, 50 mL). The combined organic layers were washed with brine (80 mL), dried

($MgSO_4$), and evaporated under reduced pressure. Silica gel chromatography (chloroform–ethanol, 100:0 → 90:10) of the residue gave **11**, isolated as a pale-yellow glass (12.86 g, ~58%); R_F 0.23 (solvent *B*). N.m.r. data: ^1H [$(CD_3)_2SO$]: δ 0.9–1.25 (m, 28 H), 3.79 (m, 1 H), 3.93 (dd, 1 H, *J* 3.0 and 12.6 Hz), 4.10 (dd, 1 H, *J* 4.4 and 12.6 Hz), 4.50 (m, 1 H), 4.57 (m, 1 H), 5.78 (d, 1 H, *J* 5.8 Hz), 6.20 (d, 1 H, *J* 6.5 Hz), 7.27 (bs, 2 H), 8.03 (s, 1 H), 8.12 (s, 1 H); ^{13}C ($CDCl_3$): δ 12.44, 12.95, 13.10, 13.55, 16.93, 16.98, 17.08, 17.37, 17.43, 17.53, 61.51, 74.41, 76.18, 81.31, 83.91, 119.27, 139.73, 149.26, 152.40, 155.77.

6-N-Benzoyl-9-[3,5-O-(1,1,3,3-tetra-isopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]adenine (**12**). — Benzoyl chloride (11.2 mL, 96.5 mmol) was added to a stirred, cooled (ice–water) solution of **11** (9.3 g, ~18.2 mmol) in dry pyridine (128 mL), and the reactants were allowed to warm up to room temperature. After 16 h, water (5 mL) was added and, after a further 35 min, the mixture was concentrated under reduced pressure. A solution of the residual syrup in dichloromethane (200 mL) was extracted with saturated aqueous sodium hydrogen carbonate (400 mL). The aqueous layer was back-extracted with dichloromethane (2 × 60 mL), and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Toluene was evaporated from the residue five times under reduced pressure. To a solution of the glassy residue in ethanol (158 mL) at ~0° was added methanolic 30% sodium methoxide (22.3 mL, ~0.117 mol). After 20 min, pyridine (12 mL) and glacial acetic acid (8 mL) were added, and the products were concentrated under reduced pressure. A solution of the residue in dichloromethane (200 mL) was extracted with water (170 mL), the aqueous extract was back-extracted with dichloromethane (2 × 40 mL), and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Silica gel chromatography (chloroform–ethanol, 100:0→95:5) of the residue gave the crude product (10.42 g, ~93%) which was used without further purification. Crystallisation of this material from acetonitrile gave **12** as colourless needles, m.p. 103–105°; R_F 0.39 (solvent *B*). N.m.r. data: ^1H [$(CD_3)_2SO$], δ 0.95–1.25 (m, 28 H), 3.85 (m, 1 H), 3.95 (dd, 1 H, *J* 2.9 and 12.6 Hz), 4.14 (dd, 1 H, *J* 4.6 and 12.6 Hz), 4.60 (m, 2 H), 5.87 (d, 1 H, *J* 5.6 Hz), 6.38 (d, 1 H, *J* 6.2 Hz), 7.55 (m, 2 H), 7.63 (m, 1 H), 8.06 (d, 2 H, *J* 7.2 Hz), 8.33 (s, 1 H), 8.70 (s, 1 H), 11.20 (bs, 1 H); ^{13}C ($CDCl_3$): δ 12.49, 13.02, 13.14, 13.50, 16.99, 17.07, 17.37, 17.41, 17.45, 17.52, 61.95, 76.03, 76.99, 81.70, 83.65, 122.16, 128.06, 128.72, 132.71, 133.55, 142.84, 148.88, 151.38, 152.21, 164.94 (Found: C, 56.5; H, 7.0; N, 11.2. $C_{29}H_{43}N_5O_6Si_2$ calc.: C, 56.7; H, 7.1; N, 11.4%).

6-N-Benzoyl-9-[3,5-O-(1,1,3,3-tetra-isopropyldisiloxane-1,3-diyl)-2-O-trifluoromethanesulfonyl-β-D-arabinofuranosyl]adenine (**12a**). — A solution of **12** (4.31 g, ~7.0 mmol) in dry dichloromethane was evaporated under reduced pressure. This process was repeated twice more, and trifluoromethanesulfonic anhydride (1.77 mL, 10.5 mmol) was added during 20 min to a dry, stirred solution of the residue in dichloromethane (12 mL) and pyridine (12 mL) at −15° under nitrogen. The mixture was allowed to warm up to 10° during 2 h, then kept at 10° for 3 h, poured into ice-cold saturated aqueous sodium hydrogen carbonate (150 mL), and extracted with dichloromethane (120 mL, followed by 2 × 20 mL). The combined extracts were washed with

saturated aqueous sodium hydrogen carbonate (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Toluene was evaporated from the residue. Silica gel chromatography (1:1 dichloromethane–hexane, dichloromethane, and 8:1 → 4:1 dichloromethane–ethyl acetate) of the resulting orange-coloured glass gave **12a**, isolated as a pale-yellow glass (4.24 g, ~81%); R_f 0.56 (solvent *B*), 0.37 (solvent *E*). ^{1}H-N.m.r. data ($CDCl_3$): δ 0.9–1.3 (m, 28 H), 3.99 (m, 1 H), 4.10 (dd, 1 H, *J* 3.2 and 12.4 Hz), 4.24 (dd, 1 H, *J* 5.8 and 12.4 Hz), 5.42 (m, 1 H), 5.52 (m, 1 H), 6.47 (d, 1 H, *J* 6.0 Hz), 7.5–7.65 (m, 3 H), 8.03 (m, 2 H), 8.13 (s, 1 H), 8.81 (s, 1 H), 9.11 (bs, 1 H).

Reaction between **12a** *and AXT (***7b***) in the presence of base, followed by treatment with tetraethylammonium fluoride and ammonia.* — (*a*) Dry N^1,N^1,N^2,N^2-tetramethylguadinine (0.63 mL, 5.0 mmol) was added dropwise to a stirred mixture of **12a** (2.54 g, ~3.4 mmol) and AXT (**7b**; 2.16 g, 6.74 mmol) in dry methyl sulfoxide (25 mL) under nitrogen at room temperature. After 2 h, chilled chloroform (250 mL) was added and the mixture was extracted with saturated aqueous sodium hydrogen carbonate (200 mL). The aqueous layer was back-extracted with chloroform (50 mL), and the combined organic layers were washed with water (4 × 100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Silica gel chromatography (2:1 dichloromethane–hexane, dichloromethane, and 4:1 dichloromethane–ethyl acetate) of the residue gave a pale-coloured glass. A solution of ~M tetraethylammonium fluoride in acetonitrile (13.6 mL) was added to this product, the solution was stirred at room temperature for 15 min, then concentrated under reduced pressure, and the residue was dissolved in methanolic ~8M ammonia (50 mL) at room temperature. After 24 h, the mixture was evaporated under reduced pressure. Silica gel chromatography (chloroform–ethanol, 98:2 → 95:5) of the residue and crystallisation from acetonitrile gave 2′-*S*-[9-(4-methoxyphenyl)xanthen-9-yl]-2′-thioadenosine (**13**; 1.481 g, ~76%) as colourless needles, m.p. 141–143°, R_f 0.54 (solvent *C*). N.m.r. data [$(CD_3)_2SO$]: ^{1}H, δ 3.34 (m, 2 H), 3.47 (m, 1 H), 3.69 (s, 3 H), 3.80 (dd, 1 H, *J* 4.3 and 9.8 Hz), 3.91 (m, 1 H), 5.35 (d, 1 H, *J* 4.2 Hz), 5.85 (d, 1 H, *J* 9.8 Hz), 5.91 (dd, 1 H, *J* 2.9 and 9.4 Hz), 6.42 (m, 1 H), 6.65–6.85 (m, 5 H), 6.95–7.15 (m, 4 H), 7.23 (m, 1 H), 7.34 (m, 3 H), 7.89 (s, 1 H), 7.97 (s, 1 H); ^{13}C, δ 51.62, 55.05, 55.19, 62.26, 71.92, 88.45, 113.46, 115.20, 116.09, 120.25, 122.39, 123.19, 124.78, 124.99, 128.01, 128.78, 128.98, 130.73, 138.17, 140.28, 147.91, 149.52, 149.87, 151.51, 156.26, 157.90 (Found: C, 62.5; H, 4.7; N, 12.2; S, 5.7. $C_{30}H_{27}N_5O_5S{\cdot}0.25H_2O$ calc.: C, 62.8; H, 4.8; N, 12.2; S, 5.6%).

(*b*) Dry triethylamine (0.30 mL, 2.15 mmol) was added to a stirred mixture of **12a** (1.068 g, 1.43 mmol), AXT (**7b**; 1.83 g, 5.71 mmol), and dry methyl sulfoxide (10 mL) with no special precautions being taken to exclude atmospheric oxygen. After 32 h, the mixture was partitioned between dichloromethane (100 mL) and saturated aqueous sodium hydrogen carbonate (70 mL). The aqueous layer was back-extracted with dichloromethane (20 mL), and the combined organic layers were washed with water (5 × 40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Silica gel chromatography (1:1 dichloromethane–hexane, dichloromethane, and dichloromethane–ethyl acetate, 9:1 → 4:1) of the residue gave the nucleoside products as a pale-coloured glass to which ~M tetraethylammonium fluoride in acetonitrile (6 mL) was added. The solution

was stirred at room temperature for 15 min, then concentrated under reduced pressure, and the residue was dissolved in methanolic ~8M ammonia (20 mL) at room temperature. After 22 h, the solvents were evaporated under reduced pressure. Silica gel chromatography (chloroform–ethanol, 99:1) of the residue gave a product with R_F 0.54 (solvent *C*), which was crystallised from acetonitrile to give **13** (0.114 g, ~14%) that was identical (t.l.c., ^{1}H- and ^{13}C-n.m.r. spectra) to the compound in (*a*) above. Elution with chloroform–ethanol (97:3) gave a product, with R_F 0.43 (solvent *C*), that was crystallised from acetonitrile to give 2′-deoxy-2′-[9-(4-methoxyphenyl)xanthen-9-yldithio]adenosine (**16**; 0.298 g, 35%) as colourless crystals, m.p. 177° (dec.), R_F 0.43 (solvent *C*). N.m.r. data [$(CD_3)_2SO$]: ^{1}H, δ 2.75 (dd, 1 H, *J* 5.3 and 8.1 Hz), 3.42 (m, 2 H), 3.76 (s, 3 H), 3.82 (m, 1 H), 3.95 (m, 1 H), 5.20 (dd, 1 H, *J* 4.4 and 7.1 Hz), 5.82 (d, 1 H, *J* 5.2 Hz), 6.01 (*d*, 1 H, *J* 8.2 Hz), 6.50 (dd, 1 H, *J* 1.4 and 7.9 Hz), 6.8–7.3 (m, 11 H), 7.35 (bs, 2 H), 8.02 (s, 1 H), 8.18 (s, 1 H); ^{13}C, δ 55.03, 55.70, 59.79, 61.63, 72.07, 87.27, 89.76, 113.58, 115.65, 115.86, 119.55, 122.79, 123.17, 123.34, 124.33, 128.86, 129.26, 129.38, 129.72, 130.30, 134.72, 139.53, 148.90, 150.14, 150.48, 152.38, 156.09, 158.18 (Found: C, 59.8; H, 4.45; N, 11.7; S, 10.8. $C_{30}H_{27}N_5O_5S_2$ calc.: C, 59.9; H, 4.5; N, 11.6; S, 10.7%).

Reaction between **16** *and triphenylphosphine*. — A mixture of triphenylphosphine (0.066 g, 0.25 mmol), **16** (0.126 g, 0.21 mmol), and glacial acetic acid (1.5 mL) was stirred at 50° under nitrogen for 2 h, and then concentrated under reduced pressure. A solution of the residue in ethanol was evaporated under reduced pressure and this process was repeated twice. Silica gel chromatography (chloroform–ethanol, 100:0 → 95:5) of the residue and crystallisation from acetonitrile gave **13** (0.090 g, 75%), identical to the product described above.

2′-Thioadenosine (**1c**). — A solution of **13** (0.433 g, 0.76 mmol) and freshly distilled pyrrole (0.53 mL, 7.6 mmol) in redistilled glacial acetic acid (3.3 mL) was stirred under nitrogen at 70° for 1 h, and then concentrated under reduced pressure (water-pump, followed by oil-pump). The colourless gummy residue was shaken vigorously with dry dichloromethane (15 mL), and the mixture was then kept at 4° and filtered. The residue (0.168 g, 78%) was washed with dichloromethane and dried *in vacuo* at room temperature. Crystallisation from methanol gave **1c** as colourless prisms, m.p. >150° (dec.), $[\alpha]_D^{20}$ −92° (*c* 0.59, methyl sulfoxide); R_F 0.31 (solvent *D*), 0.71 (solvent *F*). N.m.r. data [CD_3CO_2D]: ^{1}H, 3.92 (dd, 1 H, *J* 1.9 and 12.8 Hz), 4.00 (dd, 1 H, *J* 2.0 and 12.8 Hz), 4.09 (dd, 1 H, *J* 4.9 and 9.2 Hz), 4.38 (s, 1 H), 4.53 (d, 1 H, *J* 5.0 Hz), 5.97 (d, 1 H, *J* 9.2 Hz), 8.31 (s, 1 H), 8.37 (s, 1 H); ^{13}C [$(CD_3)_2SO$], δ 44.64, 61.91, 72.30, 87.42, 90.09, 119.36, 140.05, 149.14, 152.42, 156.14 (Found: C, 42.45; H, 4.7; N, 24.5; S, 11.05. $C_{10}H_{13}N_5O_3S$ calc.: C, 42.4; H, 4.6; N, 24.7; S, 11.3%).

2′-S,3′-O-Isopropylidene-2′-thioadenosine (**14**). — Dry acetonitrile (3.5 mL) and 2,2-dimethoxypropane (1.4 mL, 11.4 mmol) were added in turn to a mixture of **1c** (0.156 g, 0.55 mmol) and toluene-4-sulfonic acid monohydrate (0.133 g, 0.70 mmol), and the mixture was stirred rapidly at room temperature. After 1 h, methanolic ~8M ammonia (2.0 mL) was added, the mixture was evaporated under reduced pressure, and the residue was partitioned between dichloromethane (25 mL) and water (12 mL). The aqueous layer was back-extracted with dichloromethane (3 × 5 mL), and the combined

organic layers were washed with water (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Water (0.2 mL) was added to a solution of the residual glass in acetic acid (1.0 mL) at room temperature, and the mixture was concentrated under reduced pressure. Silica gel chromatography (chloroform–ethanol, 97:3) of the residue and crystallisation from ethanol gave **14** (0.121 g, 68%), m.p. 213–214.5°; R_f 0.56 (solvent *C*). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 1.66 (s, 3 H), 1.78 (s, 3 H), 3.69 (m, 2 H), 4.32 (m, 1 H), 4.81 (dd, 1 H, *J* 5.1 and 7.7 Hz), 5.01 (d, 1 H, *J* 5.2 Hz), 5.61 (dd, 1 H, *J* 4.9 and 6.9 Hz), 6.04 (d, 1 H, *J* 7.8 Hz), 7.42 (bs, 2 H), 8.15 (s, 1 H), 8.39 (s, 1 H); ^{13}C, δ 30.81, 31.07, 54.53, 61.81, 83.57, 88.23, 92.86, 95.56, 119.31, 139.76, 148.91, 152.55, 156.18 (Found: C, 48.6; H, 5.2; N, 21.4. $C_{13}H_{17}N_5O_3S$ calc.: C, 48.3; H, 5.3; N, 21.7%).

Bis(2′-deoxyadenosin-2′-yl) disulfide (**15**). — A solution of iodine (0.031 g, 0.122 mmol) in ethanol (2 mL) was added dropwise during 5 min to a stirred solution of **1e** (0.073 g, 0.26 mmol) in ethanol (3 mL), water (0.75 mL), and pyridine (0.25 mL) at room temperature. Methanol (5 mL) and water (3 mL), followed by Amberlite IRA-400 (AcO^-) resin (~3.5 mL), were added to the products. After 1 h, the resin was removed by filtration and washed with methanol–water (5:3). The combined filtrate and washings were evaporated under reduced pressure and the residue was crystallised from water to give **15** (0.058 g, 80%), m.p. 150° (from methanol); R_f 0.14 (solvent *D*), 0.63 (solvent *F*). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 3.51 (m, 2 H), 3.61 (m, 2 H), 3.91 (m, 2 H), 4.11 (m, 2 H), 4.32 (dd, 2 H, *J* 5.2 and 8.4 Hz), 5.35 (dd, 2 H, *J* 4.8 and 8.4 Hz), 5.76 (d, 2 H, *J* 4.9 Hz), 6.14 (d, 2 H, *J* 8.4 Hz), 7.34 (bs, 4 H), 8.13 (s, 2 H), 8.32 (s, 2 H); ^{13}C, δ 54.94, 61.58, 72.23, 87.21, 88.52, 119.36, 139.88, 149.20, 152.39, 156.01 (Found: C, 42.4; H, 4.6; N, 23.4. $C_{20}H_{24}N_{10}O_5S_2 \cdot CH_3OH$ calc.: C, 42.3; H, 4.7; N, 23.5%).

9-{2-S-[9-(4-methoxyphenyl)xanthen-9-yl]-2-thio-β-D-arabinofuranosyl}adenine (**20**). — A solution of 1,3-dichloro-1,1,3,3-tetra-isopropyldisiloxane[10] (2.2 g, 7.0 mmol) in dry dichloromethane (10 mL) was added dropwise during 50 min to a stirred solution of 6-*N*-benzoyladenosine (2.51 g, 6.8 mmol) in dry pyridine (20 mL) at room temperature. After 2 h, methanol (5 mL) was added, the mixture was concentrated under reduced pressure, and the residue was partitioned between dichloromethane (100 mL) and saturated aqueous sodium hydrogen carbonate (100 mL). The aqueous layer was back-extracted with dichloromethane (30 mL), and the combined organic layers were washed with water (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Silica gel chromatography (chloroform–ethanol, 97:3) of the residue gave a colourless glass (3.29 g), R_f 0.37 (solvent *A*).

The above material (2.85 g, ~4.6 mmol) was treated with trifluoromethanesulfonic anhydride (1.15 mL, 6.8 mmol) in pyridine (8 mL) and dichloromethane (8 mL) at −10° as described above for **12**. Following work-up and chromatography, the triflate was isolated as a colourless glass (3.10 g); R_f 0.54 (solvent *A*). A portion of this triflate (1.58 g, ~2.12 mmol) was allowed to react with AXT (**7b**; 2.587 g, 8.07 mmol) and N^1,N^1,N^3,N^3-tetramethylguanidine (0.50 mL, 4.0 mmol) in methyl sulfoxide (12 mL) for 24 h at room temperature under the conditions described above for **13**. The mixture was worked-up and treated first with ~M tetraethylammonium fluoride in acetonitrile (10 mL) at room temperature for 20 min and then with methanolic 8M ammonia (20 mL) at

room temperature for 24 h. Silica gel chromatography (chloroform–ethanol, 100:0 → 95:5) of the product gave amorphous **20** (0.444 g, 26%, based on 6-*N*-benzoyladenosine), R_F 0.40 (solvent *C*). N.m.r. data [$(CD_3)_2SO$]; ^1H, δ 3.45 (dd, 1 H, *J* 7.5 and 8.9 Hz), 3.57 (m, 3 H), 3.74 (s, 3 H), 4.54 (m, 1 H), 4.87 (m, 1 H), 5.49 (d, 1 H, *J* 7.3 Hz), 5.72 (d, 1 H, *J* 6.0 Hz), 6.59 (dd, 1 H, *J* 1.5 and 7.9 Hz), 6.75–6.9 (m, 3 H), 7.05–7.25 (m, 6 H), 7.27 (bs, 2 H), 7.37 (m, 3 H), 8.03 (s, 1 H); ^{13}C, δ 53.55, 54.99, 55.42, 60.88, 72.89, 83.84, 84.09, 113.35, 115.98, 116.22, 118.97, 123.19, 123.54, 125.28, 125.95, 128.80, 129.38, 129.78, 130.32, 135.71, 139.98, 148.54, 149.80, 150.26, 151.92, 155.84, 158.06 (Found: C, 62.7; H, 4.7; N, 12.2; S, 5.7. $C_{30}H_{27}N_5O_5S \cdot 0.2H_2O$ calc.: C, 62.9; H, 4.8; N, 12.2; S, 5.6%).

*9-(2-Thio-β-*D*-arabinofuranosyl)adenine* (**5**). — A solution of **20** (0.286 g, 0.50 mmol) and freshly distilled pyrrole (0.30 mL, 4.3 mmol) in redistilled glacial acetic acid (2.2 mL) was stirred under nitrogen at 70° for 40 min, then cooled and evaporated to dryness under reduced pressure. The residue was triturated with dichloromethane (25 mL) that contained 2 drops of 2-mercaptoethanol, and recrystallised from methanol to give **5** (0.102 g, 72%), m.p. 211–212° (dec.) [lit.[6] m.p. 210–212° (dec.), $[\alpha]_D^{20}$ −72° (*c* 0.53, methyl sulfoxide); R_F 0.23 (solvent *D*), 0.69 (solvent *F*). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 3.65–3.80 (m, 4 H), 4.28 (m, 1 H), 5.19 (m, 1 H), 5.81 (d, 1 H, *J* 5.9 Hz), 6.38 (d, 1 H, *J* 7.2 Hz), 7.30 (bs, 2 H), 8.14 (s, 1 H), 8.31 (s, 1 H); ^{13}C, δ 47.71, 59.74, 74.40, 84.14, 84.52, 118.43, 139.45, 149.14, 152.41, 155.92 (Found: C, 42.6; H, 4.6; N, 24.4; S, 11.4. $C_{10}H_{13}N_5O_3S$ calc.: C, 42.4; H, 4.6; N, 24.7; S, 11.3%).

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